Exhibit 158, part 1

Response to FDA Request for Information on Talc
Johnson & Johnson Consumer Inc.

Johnson & Johnson
CONSUMER INC.

March 17, 2016

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
ATTN: Theresa Michele, MD, Director, Division of Nonprescription Drug Products, ODE IV

Re: Response to FDA Request for Information on Talc

Dear Dr. Michele:

This submission is our written response to the following email request from CAPT Janice Adams-King, MSN, CRNP, CPHN (USPHS), Safety Regulatory Project Manager, Office of Drug Evaluation IV, Division of Nonprescription Drug Products (DNDP), Center for Drug Evaluation and Research (CDER), dated 25 February 2016: "Please provide all safety literature and data regarding talc, including data in support of the safety of this active ingredient and data that shows potential harmful effects for this active ingredient, by March 17, 2016."

Following a recent jury verdict in a case that was heard in the City of St Louis, Missouri Circuit Court, concerning the use of talc and ovarian cancer, Johnson & Johnson Consumer Inc. (JJCI) contacted Capt. Janice Adams-King on 25 February 2016 to seek guidance on whom to talk to regarding this verdict, so that we could inform the agency about JJCI's position regarding the verdict; offer our support to the agency by contributing relevant talking points in the event that the agency intended to issue a public statement regarding this verdict; and answer any questions the agency might have regarding this verdict. In addition, we noted that this JJCI strongly disagrees with the outcome of this litigation and plans to ask the court to overturn this decision through post-trial proceedings, including the appellate process if necessary.

At Ms. Adams-King's suggestion, JJCI immediately contacted Dr. Nakissa Sadrieh, Director, Cosmetics Staff, Office of Cosmetics and Colors (OCAC), Center for Food Safety and Applied Nutrition via a phone call, followed by an email memo. Later on the same day (25 February 2016), DNDP requested a teleconference with JJCI, following which the referenced email request for additional information on talc was sent to JJCI.

Johnson & Johnson Consumer Inc.
199 Grandview Road, Skillman, NJ 08558 (908) 874-1702

Response to FDA Request for Information on Talc

This submission is our response to the referenced email request and includes a summary of key published reviews of talc safety and ovarian cancer, relevant post-marketing talc safety data, and information on chemistry, manufacturing, and controls.

This submission is being provided on compact disk. As the size of this submission is over 20 MB, we are unable to transmit the submission via email, given our company's email message size restriction of 10 MB for inbound and outbound messages.

If you have any questions, please contact me at 908-874-1702 or by email at jekuta@its.jnj.com.

Sincerely,

Jethro Ekuta

Digitally signed by Jethro Ekuta
DN: c=US, o=JNJ, ou=Employees, ou=1018932, cn=Jethro Ekuta, email=JEkuta@ITS.JNJ.com
Reason: I am the author of this document.
Date: 2016.03.15 17:19:15 -04'00'
Adobe Acrobat version: 11.0.10

Jethro Ekuta, D.V.M., Ph.D., RAC, FRAPS
Vice President, Regulatory Affairs North America
Johnson & Johnson Consumer Inc.

cc: CAPT Janice Adams-King, MSN, CRNP, CPHN (USPHS) – 15 CD Copies
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Response to FDA Request for Information on Talc

Johnson & Johnson Consumer Inc.

17 March 2016

Confidentiality Statement

The data and information contained in this submission constitute trade secrets and confidential commercial information (see 21 C.F.R. 20.61). Johnson & Johnson Consumer Inc. hereby claims the legal protections afforded such trade secret and confidential information under 5.U.S.C. 552(b), 21 U.S.C. 331(j) and 18 U.S.C. 1905. Further dissemination may only be made with the express written permission of Johnson & Johnson Consumer Inc.

Table of Contents

1 INTRODUCTION

Johnson & Johnson Consumer Inc. (JJCI) contacted FDA (Janice Adams-King, Division of Nonproprietary Drug Products, DNDP, Center for Drug Evaluation and Research and Nakissa Sadrieh, Office of Cosmetics and Colors, OCAC, Center for Food Safety and Applied Nutrition) on 25 February 2016 following a jury verdict in a case concerning the use of talc and ovarian cancer. This case was heard in the City of St Louis, Missouri Circuit Court; JJCI strongly disagrees with the outcome of this litigation and plans to ask the court to overturn this decision through post-trial proceedings, including the appellate process if necessary. DNDP scheduled a teleconference with the Company for 25 February 2016, and following the teleconference that same day, DNDP sent an email to JJCI requesting the following: "Please provide all safety literature and data regarding talc, including data in support of the safety of this active ingredient and data that shows potential harmful effects for this active ingredient, by March 17, 2016."

This response is based on JJCI's understanding of FDA's request and includes a summary of key published reviews of talc safety and ovarian cancer (Section 2), recent post-marketing talc safety data, and information on chemistry, manufacturing, and controls (Section 3). Please note that talc is inactive, ie, not a pharmacologically active ingredient, and is a major component in many body powders such as Johnson's® Baby Powder and Shower to Shower® Powder, which are classified as cosmetics per regulation.

Various governmental and non-governmental agencies as well as other expert panels have examined whether talc is a carcinogen, and none have concluded that it is a carcinogen. Many countries have allowed the use of talc, among them the United States, those in the European Union (EU), Canada, Argentina, Brazil, China, India, Israel, South Africa, Turkey, and Indonesia.

There are a number of local monographs which define standards for talc used in both drug formulas and cosmetic body powders. Examples of countries that regulate talc in cosmetics include the US, EU, China, Canada, UK, and Brazil. The US FDA lists talc as Generally Recognized as Safe (GRAS) for use in foods and Generally Recognized as Safe and Effective (GRASE) for drugs. It is also listed as a color additive that may be used in coloring drug products and as a component of colors for use in drugs and cosmetics. Talc used in JJCI body powders meets pharmaceutical specifications as established by the European and US Pharmacopoeia.

2 SAFETY LITERATURE REVIEWS

2.1 Governmental and Nongovernmental Agency Reviews

2.1.1 US Food and Drug Administration (FDA)

FDA provided a review of talc safety in its 01 April 2014 response letter [1] to Dr. Epstein's 1994 and 2008 Citizen Petitions [2,3]. FDA's letter informed Dr. Epstein that his 1994 and 2008 Citizen Petitions, along with his request for a hearing, were denied because: "FDA did not find that the data submitted presented conclusive evidence of a causal association between talc use in the perineal area and ovarian cancer." In addition to reviews of epidemiologic and toxicologic studies (see Section 2.3 and Section 2.4, respectively), FDA summarized its 2009 exploratory survey of marketed cosmetic-grade raw material talc and finished cosmetic products containing talc, including JJCI products (Johnson's® Baby Powder and Shower to Shower® Morning Fresh Absorbent Body Powder). FDA indicated that no asbestos fibers or structures were found in samples of cosmetic-grade raw material talc or cosmetic products containing talc including eye shadow, blush, foundation, face powder, and body powder.

2.1.2 US National Toxicology Program (NTP)

Cosmetic talc is not included in the most recent (2014) Report on Carcinogens, published by the US NTP [4]. NTP is a globally-recognized program and is formed from parts of several different government agencies, including the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the FDA.

2.1.3 National Cancer Institute (NCI)

In 2016, the National Cancer Institute (NCI) updated their evidence-based summary that included a review of available information on the use of talc and ovarian cancer [5]. This included a meta-analysis of 16 studies, a pooled analysis from the Ovarian Cancer Association Consortium, a cohort study among nurses, and the prospective Women's Health Initiative. NCI concluded that the evidence is inadequate to determine whether perineal talc exposure is associated with an increased risk of ovarian cancer.

2.1.4 World Health Organization (WHO)

In 2010, the WHO International Agency for Research on Cancer (IARC) reviewed and summarized information on talc not containing asbestiform fibers [6]. The Working Group noted the following concerning cancer in experimental animals: "There is *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos

or asbestiform fibres." In addition, the Working Group noted the following concerning perineal use of talc-based body powder and cancer in humans: "There is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder." The Working Group provided the following overall evaluation: "Perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B)*." The Group 2B[1] category is used for agents for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals.

2.2 Expert Panel Reviews

2.2.1 Cosmetic Ingredient Review (CIR)

As reported in 2015 by Fiume et al, the CIR Expert Panel assessed the safety of talc for use in cosmetic products [7]. This included reviews of over 15 toxicologic studies and over 35 epidemiologic studies of genital application of talc and ovarian cancer. Epidemiologic studies reviewed included case-control studies, prospective studies, and meta-analyses. A summary of the findings are provided in the review of epidemiology and toxicology studies provided in Section 2.3 and Section 2.4, respectively.

2.3 Epidemiology Study Reviews

FDA's 2014 review [1] summarized FDA's position on epidemiologic studies evaluating the relationship of genital application of talc and ovarian cancer. In response to Dr. Epstein's Citizen Petitions, it was noted: "FDA did not find that the data submitted presented conclusive evidence of a causal association between talc use in the perineal area and ovarian cancer."

As noted previously, in 2010, the WHO IARC Working Group concluded the following concerning perineal use of talc-based body powder not containing asbestiform fibers and cancer in humans [6]: "There is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder." The Working Group provided the following overall evaluation: "Perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B)*."

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[1] Group 2B (The agent is possibly carcinogenic to humans): This category is used for agents for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals. It may also be used when there is inadequate evidence of carcinogenicity in humans but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, an agent for which there is inadequate evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

As noted previously and reported in 2015 by Fiume et al, the CIR Expert Panel assessed the safety of talc for use in cosmetic products [7]. This included a review of the epidemiologic studies of genital application of talc and ovarian cancer. Studies reviewed included case-control studies, prospective studies, and meta-analyses. A summary of the findings is provided below:

> "Numerous epidemiological studies have been performed examining the risk of ovarian cancer following talc exposure. Among the epidemiological investigations reporting statistically significant associations, the RR estimates ranged between 1.0 and 2.0 and were barely statistically significant. Many physiological, sociological, and exposure factors have been linked to ovarian cancer, a number of them with a stronger association than that of hygienic use of cosmetic talc, but causality has not been established for any of them. Most of the epidemiological studies found no trend of increasing ovarian cancer risk with increasing exposure duration or frequency or cumulative exposure, despite a 5-fold difference between the lowest and the highest exposure groups. Several of these studies reported an apparent inverse trend. The results of several epidemiological studies suggested that medical procedures expected to prevent the translocation of talc to the ovaries, such as tubal ligation or hysterectomy, reduce the RR estimates associated with talc use. Other studies found no difference in RR between women who had tubal ligation or hysterectomy and women who did not have these procedures. One study reported inverse exposure effect trends with duration of talc exposure after adjusting for tubal ligation. The use of talc-dusted condoms or diaphragms (including diaphragms known to have been stored in talc powder), which would clearly result in exposure close to the cervical opening, was not associated with an increased estimate of RR of ovarian cancer."

Table 1 provides a listing of publications of epidemiologic studies of genital talc use and ovarian cancer identified after the CIR (Fiume et al) [7]. The table includes the last name of the first author of the publication, the year of publication, the study design, and the reference number in this submission. In addition, the table provides the extent to which the publication included studies [with reference numbers from the current submission noted] which were previously reported in the CIR. The results of the studies are summarized following the table.

Table 1. Publications of Epidemiologic Studies of Genital Talc Use and Ovarian Cancer Identified after the CIR (Fiume et al) [7]

First Author of Publication	Year Published	Study Design	Reference Number	Data previously reported in CIR (Fiume et al.)
Houghton et al.	2014	Prospective	[8]	No
Gates et al.	2010	Prospective	[9]	Yes, partially as [10]
Wu et al.	2015	Pooled case-control	[11]	Yes, partially as [12]
Terry et al.	2013	Pooled case-control	[13]	Yes, partially as [14,15,16,17,18]
Cramer et al.	2016	Pooled case-control	[19]	Yes, partially as [14,20,21]

Two additional prospective studies have been reported [8,9]. It should be noted that prospective cohort studies do not suffer from recall bias which is always a concern in case-control studies, especially those in which long-term exposure is a hypothesized risk factor. One recent prospective study in the Women's Health Initiative Observational Study cohort was reported by Houghton et al in 2014 [8]. This comprehensive study of 61,576 post-menopausal women with a mean follow-up of 12.4 years assessed long-term use of perineal powder. The study examined different types of use (genital, on sanitary napkins, and on diaphragms), all possible combinations of use, and duration of use. The study found that use of perineal powder was not associated with ovarian cancer risk, overall and by cancer type. In addition, there was no association with increasing duration of use.

Findings from the second prospective study [9] by Gates et al were reported in 2010 but appear not to have been included in the CIR reported by Fiume et al [7]. Gates et al extended the Gertig et al (2000) [10] study of the Nurses' Health Study (NHS) data by examining two cohorts of the NHS (NHS and NHSII). In addition, they extended the follow-up of the NHS from 1996 to 2006. Gates et al found there were non-significant, positive associations between talc use and overall ovarian cancer and by cancer type. In this analysis with the additional years of follow-up, the earlier observed increased risk in serous invasive tumors reported by Gertig [10] was no longer present.

Pooled results from a combination of four previously reported case-control studies were reported in 2015 by Wu et al [11]; at least one of the four studies [12] was included in the CIR reported by Fiume et al [7]. Similarly, in 2013, Terry et al [13] reported on a pooled analysis from eight population-based case-control studies; five [14,15,16,17,18] of which were included in the CIR. The findings of these pooled studies were consistent with results of case-control studies summarized in the CIR. Most recently, Cramer et al [19] reported on a pooled analysis from three previously reported case-control studies [14,20,13,21]. All three previously reported studies [14,20,21] were included in the CIR [7]. Vitonis et al [21] reported on a pooled analysis of all three case-control studies and was included in the CIR, although the number of cases and controls were lower than in the recent analysis [19]. In addition, one of the studies [14] was included in the pooled analysis by Terry et al [13]. The findings of the recent pooled analysis by Cramer et al [19] were consistent with the results of previously reported case-control studies, of which they were a part; in addition, a trend for increasing risk by talc-years was reported.

2.4 Toxicology Study Reviews

FDA's 2014 review [1] summarized its position on talc as a carcinogen. FDA noted serious flaws in the NTP study (the basis for Dr. Epstein's requests for carcinogenicity warnings) and cited a panel of experts at the 1994 ISRTP/FDA workshop that concluded that the 1993 NTP study had no relevance to human risk. FDA also indicated that it had reviewed the toxicity literature from 1980 to 2008 and did not find enough additional support at that time for the types of warning labels proposed by Dr. Epstein in his Citizen Petitions. In addition, in 2010, the WHO IARC Working Group [6] concluded: "There is *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibres."

As reported in 2015 by Fiume et al, the CIR Expert Panel assessed the safety of talc for use in cosmetic products [7]. Talc was found to be non-toxic by ingestion and skin exposure and demonstrated to be non-irritating and non-sensitizing to skin. In addition, animal studies have shown that talc is non-genotoxic and not a developmental toxicant.

In 1976, specifications were developed for cosmetic talc requiring that no detectable fibrous, asbestos mineral be present. This is important for any consideration of preclinical and epidemiological literature prior to 1976, as the presence of asbestos was not necessarily ascertained.

In summary, no biological effects of talc are inherent to its chemistry; it is considered chemically inert. The effects noted are due to the presence of an inert, foreign particle, notably:

- Nuisance dust by inhalation
- Granulomas when applied to open wounds
- Slight irritant to the eyes
- Chronic preclinical inhalation carcinogenicity secondary to lung overload and deemed by US FDA to be irrelevant
- Occupational - diffuse interstitial fibrosis and progressive fibrosis

In fact, this same foreign body reaction is used therapeutically in the lung (pleurodesis) in the treatment of lung collapse, where injection of talc slurry into the pleural cavity results in inflammation and adhesion of the lung to the chest wall.

Since the CIR Expert Panel review, one toxicology study has been published for talc [22]. While this study included no novel toxicology endpoints for talc, it did provide a mechanism for explaining commonly observed lesions following repeated talc exposure. Following four-week whole-body exposure for six hours per day, five days per week to Sprague-Dawley rats of up to 100 mg talc/m^3, there was infiltration of macrophages on the alveolar walls and near the terminal and respiratory bronchioles. At the highest exposure level in rats, there was an increased expression of superoxide dismutase-2, indicative of macrophage aggregation and oxidative damage. Such findings are expected in response to high exposures to a foreign particle in the lungs.

3 COMPANY SAFETY DATA REVIEWS

3.1 Chemistry, Manufacturing, and Controls

Talc is a powdered, selected, natural, hydrated magnesium silicate. Pure talc has the formula $Mg_3Si_4O_{10}(OH)_2$. It may contain variable amounts of associated minerals among which chlorites (hydrated aluminum and magnesium silicates), magnesite (magnesium carbonate), calcite (calcium carbonate), and dolomite (calcium and magnesium carbonate) are predominant. Talc is commonly used in many topical cosmetic applications, including eye shadow, blush foundation, face powder, and body powder. Both cosmetic and United States Pharmacopoeia (USP) grades are generally used for such applications.

For Body Powders, JJCI uses talc which meets the USP monograph. JJCI talc is also evaluated for a number of additional impurities. Impurity testing is summarized in Table 2.

Table 2. Impurity Testing for JJCI Body Powders

USP Impurity Testing	Additional JJCI Impurity Testing
Water Soluble Substances	Free Crystalline Silica
Iron	Chromium
Lead	Nickel
Calcium	Mercury
Aluminum	Cadmium
Asbestos	Arsenic

The USP permits the use of either Infrared Absorption or X-Ray Diffraction to evaluate for asbestos-form structures. If positive results are obtained, then Optical Microscopy is used as the definitive test. JJCI uses a combination of X-Ray Diffraction, Optical Microscopy, and Transmission Electron Microscopy (TEM).

As a second impurity check, talc used worldwide for JJCI Body Powders is periodically sent to an independent test lab for a full comparative evaluation. No asbestos-form structures have ever been found during any testing.

3.2 Post-marketing Safety Database Review

3.2.1 Current Review of Company Post-marketing Data

A review of Company post-marketing cases concerning talc-containing powder products, Johnson's® Baby Powder and Shower to Shower® Powder, was performed [23]. Shower to Shower® products were divested by the Company in 2013. After the divestiture, cases reporting the use of Shower to Shower® Powders were assigned in the Company Global Safety Database to Johnson's® Baby Powder as Company suspect or co-suspect products.

Post-marketing safety reports are collected from healthcare professionals, consumers, publications, clinical studies, and other sources. Cases are included regardless of seriousness or causality. The reporting frequency of such reports is influenced by various factors, such as consumer awareness, clinical studies, scientific interests, media reports, and legal interests. Stimulated reporting is usually seen when there are public news media reports on any particular topic of safety concern about consumer products. Increased reporting also occurs when there is a legal interest in a safety topic. Although

the Johnson's® Baby Powder products have been in use for many decades, almost all the cases noted below for ovarian cancer have been reported by or through attorneys in the last two years. Clinical review of these cases did not identify data to provide evidence to indicate a causal association between product use and ovarian cancer.

A search of the Company safety database was performed using the following criteria:

- Closed cases only
- Cases reported in the current safety database (ie, for the period September 2011 through 23 February 2016 for North America and July 2014 through 23 February 2016 for the rest of the world[2])
- Medically assessed cases with AE Medical Dictionary for Regulatory Activities (MedDRA) coding
- List of Johnson's® Baby Powder or Shower to Shower® Powder Company products searched regardless of drug role (suspect or suspect interacting or concomitant)
- Medically confirmed and medically unconfirmed cases
- All types of cases (eg, spontaneous/clinical study/registry, etc)
- Highest version (most recent complete version) of each case

The cases were reviewed in aggregate and results for all MedDRA System Organ Class (SOC) Groups are presented by SOC Group in the report [23]. While summarized in detail in the report, a brief summary of post-marketing data on ovarian cancer is presented here. Overall, 1269 cases were identified in the SOC of Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). Of the 1269 cases, the age of the patients was reported in 480 cases; the mean age was 52.1 years with a range of 14 years to 79 years. Females accounted for 99.69% of the cases. Of the 1269 cases, 1267 were reported from the US, one from Canada, and one from Germany. Two cases were reported in 2010, 1 in 2012, 4 in 2013, 391 in 2014, 840 in 2015, and 31 in 2016.

Overall, 97.9% (n=1242) of the 1269 cases in this system organ class reported a MedDRA preferred term coded to the high level term (HLT) Ovarian neoplasms malignant (excl germ cell). Of these 1242 cases, 398 were medically confirmed and 844 were medically unconfirmed. Table 3 provides the distribution of the 1242 cases by stage and histological type.

[2] Start dates for reporting vary due to different implementation dates for use of the current Company safety database.

Table 3. Distribution of Ovarian Cancers by Stage and Histological Type (N=1242)

Characteristic		Number of Cases[a]
Stage	I	68
	II	40
	III	140
	IV	43
	Not reported	952
Histological Type	Serous	42
	Endometrioid	13
	Mucinous	4
	Clear Cell	2
	Not reported	1182

a: The total number of cases is 1242. However, the number of preferred terms reported is 1243. Since the table reflects the characteristics of the reported preferred terms, the total by stage and histological type adds up to 1243.

An analysis of age-wise trending of cases reporting ovarian cancer was performed for 471 cases. The highest number of cases was seen in the age group 45 to 54 years (n=170), followed by the age group 55 to 64 years (n=136). Information on duration of product use was reported in 756 cases; the highest number of cases (n=217) was observed with a duration of use of 30 to 40 years.

The 1242 cases were analyzed for the presence of risk factors known to be associated with ovarian cancer. These risk factors (age 45 years and above, family history of cancer, previous cancer, smoking/tobacco, diabetes, obesity, and infertility) accounted for 372 cases, ie, 30% of the total cases received for ovarian cancers.

For 97.1% (n=1206) of the 1242 cases, females used the product to dust the perineal area for hygiene purposes; in the remaining cases insufficient information was provided regarding the nature of product use.

For 1072 cases, the outcome was not reported. For the remaining 170 cases, a fatal outcome was reported for 50 cases, not recovered was reported for 117 cases, and recovered/recovering was reported for three cases.

3.2.2 Routine Safety Surveillance

Routine Safety Surveillance is performed as monthly and quarterly adverse event trending of safety data for Monograph Drug, Medical Device, Cosmetic, and Commodities/Consumer goods (MDC) products held in the Company's Safety Database. Safety Surveillance physicians review each case detail and make a clinical assessment of causal association between the product and event. In all of the cases, the clinical assessment of causality was either unlikely or un-evaluable due to lack of information. A recent surveillance report for the time period 01 December 2015 to 31 December 2015 reported on this topic as follows:

> Increased reporting for malignant neoplasms associated with J&J BABY POWDER USA has been observed since January 2015 (and for JBABY BABY POWDER UNSPECIFIED USA since 2014), an observation possibly related with increased media awareness and legal activities surrounding the alleged issue of talc-based products and the development of cancer. As per the medical safety assessment completed by the Regional Medical Safety Officer in response to the persistent signals identified in the October 2015 report, it was stated: "The observation in October 2015 of ovarian cancer allegedly associated with prior talc use is neither new nor changed." It was maintained that: "Continued monitoring of the reports of the cases is justified in that, while there exists insufficient evidence to indicate any scientific basis to any causal link between talc and cancer, additional cases could provide additional data to support or refute the allegations." Hence, the associated signals are being assessed as "Still for continued monitoring".

4 SUMMARY

At Johnson & Johnson Consumer Inc., our confidence in using talc is based on more than 100 years of safe use and more than 30 years of research by independent researchers, scientific review boards and global regulatory authorities. Various agencies and governmental bodies have examined whether talc is a carcinogen, and none have concluded that it is. The scientific literature, post-market experience, and expert opinion do not support the association of talc and ovarian cancer.

5 REFERENCE LIST

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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APR 1 - 2014

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RE: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001/CP

Dear Dr. Epstein:

This letter is in response to your two Citizen Petitions dated November 17, 1994 and May 13, 2008, requesting that the Food and Drug Administration (FDA or the Agency) require a cancer warning on cosmetic talc products. Your 1994 Petition requests that all cosmetic talc bear labels with a warning such as "Talcum powder causes cancer in laboratory animals. Frequent talc application in the female genital area increases the risk of ovarian cancer." Additionally, your 2008 Petition requests that cosmetic talcum powder products bear labels with a prominent warning such as: "Frequent talc application in the female genital area is responsible for major risks of ovarian cancer." Further, both of your Petitions specifically request, pursuant to 21 CFR 10.30(h)(2), a hearing for you to present scientific evidence in support of this petition.

We have carefully considered both of your Petitions. We are committed to the protection of the public health and share your interest in reducing the risk of ovarian cancer. Current regulations state that cosmetic products shall bear a warning statement whenever necessary or appropriate to prevent a health hazard that may be associated with a product. FDA may publish a proposal to establish a regulation prescribing a warning statement on behalf of a petitioner if the petition is supported by adequate scientific basis on reasonable grounds.

After careful review and consideration of the information submitted in your Petitions, the comments received in response to the Petitions, and review of additional scientific information, this letter is to advise you that FDA is denying your Petitions. FDA did not find that the data submitted presented conclusive evidence of a causal association between talc use in the perineal area and ovarian cancer.

For this reason and for the additional reasons described below, FDA is denying your Petitions.

I. Discussion

The basis of your request, throughout both Petitions, can be summarized as comprising three major points:

1. Talc may be associated with asbestos.
2. Talc is a carcinogen based on the findings of a 1993 National Toxicology Program study.
3. Epidemiological studies confirm the causal relation between genital application of talc and ovarian cancer, and the protective effect of tubal ligation or hysterectomy, preventing the translocation of talc to the ovary.

As the points you raise in your Petitions concern the chemistry and toxicology of talc, the epidemiology associated with talc use, and the etiology of ovarian cancer, commensurate reviews were conducted to assess your request.

Chemistry Findings:

Asbestos is a known carcinogen and your first major point is that talc may be associated with asbestos. As evidence that talc cosmetic products contain asbestos, you first cite a 1968 survey of 22 talcum products that found fiber content averaging 19% in all 22 products. This author further concludes that "the fibrous material was predominantly talc but probably contained minor amounts of tremolite, anthophyllite, and chrysotile [asbestos-like fibers] as these are often present in fibrous talc mineral deposits …"

You then cite a follow up study from 1971-1975 that examined 21 samples of consumer talcums and powder and concluded that cosmetic grade talc was not used exclusively in these products. This study found the presence of asbestiform anthophyllite and tremolite, chrysotile, and quartz. From these two citations, one may infer that currently available talc-containing cosmetic products are presently contaminated with asbestos, a known carcinogen. Unfortunately, you did not present any original data on the chemical composition of talc currently being used in cosmetics talc products or data linking these findings to currently used talc.

It has been reported in the scientific literature that most talc products in world trade are impure as a result of the geological processes involved in the formation of talc deposits. Further, talc containing asbestos fibers such as tremolite asbestos or chrysotile are sometimes encountered. However, large deposits of high purity, asbestos-free talc do exist and talc purification techniques have been developed which can be used to improve talc quality. Thus, while it has been reported in the past that cosmetic talc has been contaminated with asbestos, it has been also reported that asbestos-free talc deposits do exist. In addition, techniques do exist for the purification of talc in order to improve its quality. You have not provided evidence that asbestos contaminated talc-containing cosmetic products are currently being marketed, since the data submitted is almost 40 years old.

Because safety questions about the possible presence of asbestos in talc are raised periodically, in 2009 FDA conducted an exploratory survey of currently marketed cosmetic-grade raw material talc and finished cosmetic products containing talc. This survey analyzed cosmetic-grade raw material talc from four suppliers out of a possible group of nine suppliers we had requested talc samples from, along with thirty-four talc-containing cosmetic products currently available in the Washington, D.C. metropolitan area for the presence of asbestos. In order to cover as broad a product range as possible, samples identified for testing included low, medium, and high priced products, along with some from "niche" markets. The cosmetic products identified as containing talc included eye shadow, blush, foundation, face powder, and body powder.

The survey found no asbestos fibers or structures in any of the samples of cosmetic-grade raw material talc or cosmetic products containing talc. While FDA found this data informative, the results were limited by the fact that only four suppliers submitted samples and by the number of products tested. They do not prove that all talc-containing cosmetic products currently marketed in the United States are free of asbestos contamination. As always, when potential public health concerns are raised, we will continue to monitor for new information and take appropriate actions to protect the public health. You may wish to see more on this survey on our website at http://www.fda.gov/Cosmetics/ProductandIngredientSafety/SelectedCosmeticIngredients/ucm293184.htm.

Toxicology Findings:

Your second major point is that talc is a carcinogen with or without the presence of asbestos-like fibers. The basis to this claim is that in 1993, the National Toxicology Program (NTP) published a study on the toxicity of non-asbestiform talc and found clear evidence of carcinogenic activity.

This NTP report concluded that cosmetic-grade talc caused tumors in animals, even though no asbestos-like fibers were found. The report made the following observations:

- There was some evidence of carcinogenic activity in non-asbestiform talc from inhalation studies in male rats based on an increased incidence of benign or malignant pheochromocytomas of the adrenal gland.
- There was clear evidence of carcinogenic activity of talc in female rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign or malignant pheochromocytomas of the adrenal gland.
- There was no evidence of carcinogenic activity of talc in male or female mice exposed to 6 or 18 mg/cubic meter.

However, this study lacks convincing scientific support because of serious flaws in its design and conduct, including:

- The investigators used micronized talc instead of consumer-grade talc resulting in the experimental protocol not being reflective of human exposure conditions in terms of particle size.

- Investigators conceded that they had problems with the aerosol generation system; whereby, the target aerosol concentrations were either excessive or not maintained during 26 of the 113-122 weeks of the study.
- The study did not include positive and negative dust controls which would have permitted an "exact assessment" of the talc's carcinogenicity relative to the two control dusts.

In light of these shortcomings, a panel of experts at the 1994 ISRTP/FDA workshop declared that the 1993 NTP study has no relevance to human risk.

In addition, we reviewed relevant toxicity literature (consisting of 15 articles from 1980 to 2008), not cited in your Petitions, to determine if there was additional support at this point in time to for your suggested warning label. Scientific literature on studies of acute exposure effects, subchronic exposure effects, chronic exposure or carcinogenicity effects, developmental or reproductive toxicity, and genotoxicity effects were reviewed. As a result of the review of this relevant literature, FDA did not find enough additional support at this point in time for your suggested warning label.

Epidemiology and Etiology Findings:

Your third major point is that epidemiological studies confirm the causal relation between genital application of talc and ovarian cancer, and the protective effect of tubal ligation or hysterectomy, preventing the translocation of talc to the ovary.

After consideration of the scientific literature submitted in support of both Citizen Petitions, FDA found:

1. The exposure to talc is not well-characterized; it is not known if the talc referred to in the scientific studies was free of asbestos contamination; various consumer brands or lots of talc were not identified; and contamination of talc by asbestiform minerals or other structurally similar compounds was not ruled out.

2. Several of the studies acknowledge biases in the study design and no single study has considered all the factors that potentially contribute to ovarian cancer, including selection bias and/or uncontrolled confounding that result in spurious positive associations between talc use and ovarian cancer risk.

3. Results of case-controls studies do not demonstrate a consistent positive association across studies; some studies have found small positive associations between talc and ovarian cancer but the lower confidence limits are often close to 1.0 and dose-response evidence is lacking.

4. A cogent biological mechanism by which talc might lead to ovarian cancer is lacking; exposure to talc does not account for all cases of ovarian cancer; and

5 there was no scientific consensus on the proportion of ovarian cancer cases that may be caused by talc exposure.

6 The conclusion of the International Agency for Research on Cancer that epidemiological studies provide limited evidence for the carcinogenicity of perineal use of talc based body powder and the IARC classification of body-powder talc as group-2B, a possible carcinogen to human beings, is persuasive, but the results of the Nurses' Health Study, a large prospective cohort study, revealed no overall association with ever talc use and epithelial ovarian cancer.

Per the etiology review, approximately 10% of epithelial ovarian cancers are associated with inherited mutations. The remaining 90% of epithelial ovarian cancers are not related to these genetic mutations are non-hereditary. They have been historically classified based on histology as borderline/low malignant potential, serous, endometrioid, mucinous, and clear-cell.

Two theories have historically dominated on the cause of epithelial ovarian cancer and these are the "incessant ovulation hypothesis" and the "gonadotropin hypothesis." In addition to these endogenous factors, the role of exogenous factors via retrograde transport of noxious substances (e.g. carcinogens, particulates such as talc and asbestos, endometriosis and infectious agents) from the vagina and uterus into the Fallopian Tubes and peritoneal cavity have been studied extensively as a possible risk factor for ovarian cancer.

While there exists no direct proof of talc and ovarian carcinogenesis, the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable. It is, therefore, plausible that perineal talc (and other particulate) that reaches the endometrial cavity, Fallopian Tubes, ovaries and peritoneum may elicit a foreign body type reaction and inflammatory response that, in some exposed women, may progress to epithelial cancers. However, there has been no conclusive evidence to support causality.

The best evidence for an association or causal relationship between genital talc exposure and ovarian cancer comes from epidemiologic data which show a statistically significant but modest increased risk of epithelial ovarian cancer, especially with serous histology, among women with a history of genital dusting with talcum powder. While the growing body of evidence to support a possible association between genital talc exposure and serous ovarian cancer is difficult to dismiss, the evidence is insufficient for FDA to require as definitive a warning as you are seeking.

Request for hearing

In addition to your request for a warning label, you also requested a hearing, under 21 CFR 10.30(h)(2), so that you can present scientific evidence in support of your petitions.

Under this regulation, FDA may deny a citizen petition request for a hearing if the data and information submitted (even if accurate), are insufficient to justify the determination urged. In consideration of your request, we conducted an expanded literature search dating from the filing of the petition in 2008 through January 2014. The results of this search failed to identify any new compelling literature data or new scientific evidence.

Since we find that the data and information are insufficient to justify the determination you request and we did not identify any new compelling literature data or new scientific evidence, FDA is also denying your hearing request.

II. Conclusion

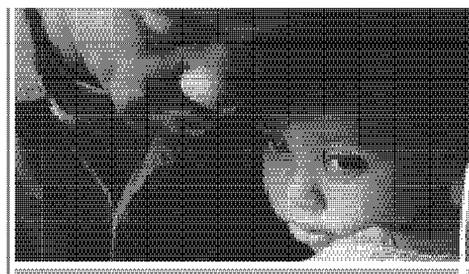
FDA appreciates the goals of the Cancer Prevention Coalition and FDA supports the goal of reducing the rate of ovarian cancer. Although FDA is denying the Cancer Prevention Coalition's petitions for the reasons discussed above, the Agency shares your commitment to the public health.

Sincerely,

Steven M. Musser, Ph.D.
Deputy Director for Scientific Operations
Center for Food Safety
and Applied Nutrition

Response to FDA Request for Information on Talc
Johnson & Johnson Consumer Inc.

Drafted: J. Gasper, OCAC, 2/28/14
Comments: L. Katz, OCAC, 3/3/14
Revised: J. Gasper, OCAC, 3/4/14
Cleared: N.Sadrieh, OCAC, 3/4/14
Cleared: LMKatz, OCAC, 3/5/14
Reviewed: FHogue, OCAC: 3/614
Cleared by:Musser:3/13/14
F/T:SRussell, OCAC 3/18/14



Citizen Petition Seeking Carcinogenic Labeling on All Cosmetic Talc Products

November 17, 1994

David A. Kessler, M.D.
Commissioner
Food and Drug Administration, Room 1- 23
12420 Parklawn Drive
Rockville, MD 20857

The undersigned submits on behalf of the Cancer Prevention Coalition, Inc. (CPC), Samuel S. Epstein, M.D., Chair and National Advisor of the Ovarian Cancer Early Detection and Prevention Foundation (OCEDPF), Nancy Nehls Nelson, member of the Ovarian Cancer Early Detection and Prevention Foundation, Peter Orris, M.D. and Quentin Young, M.D. This citizen petition is based on scientific papers dating back to the 1960s which warn of increased cancer rates resulting from frequent exposure to cosmetic grade talc.

The undersigned submits this petition under 21 U.S.C. 321 (n), 361, 362, and 371 (a); and 21 CFR 740.1, 740.2 of 21 CFR 10.30 of the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs to require that all cosmetic talc products bear labels with a warning such as Talcum powder causes cancer in laboratory animals. Frequent talc application in the female genital area increases risk of ovarian cancer.

A. AGENCY ACTION REQUESTED

This petition requests that FDA take the following action:

(1) Immediately require cosmetic talcum powder products to bear labels with a warning such as Talcum powder causes cancer in laboratory animals. Frequent talc application in the female genital area increases the risk of ovarian cancer.

(2) Pursuant to 21 CFR 10.30 (h) (2), a hearing at which time we can present our scientific evidence.

B. STATEMENT OF GROUNDS

Ovarian cancer is the fourth deadliest women's cancer in the U.S., striking approximately 23,000 and killing approximately 14,000 women this year. Ovarian cancer is very difficult to detect at the early stages of the disease, making the survival rate very low. Only three percent of ovarian cancer cases can be attributed to family history. (1) One of the avoidable risk factors for ovarian cancer is the daily use of talcum powder in the genital area. (2)

Research done as early as 1961 has shown that particles, similar to talc

and asbestos particles, can translocate from the exterior genital area to the ovaries in women. (3,4,5) These findings provide support to the unexpected high rate of mortality from ovarian cancer in female asbestos workers. (6,7,8) Minute particles, such as talc are able to translocate through the female reproductive tract and cause foreign body reactions in the ovary.

There is a large body of scientific evidence, dating back thirty years, on the toxicity and mineralogy of cosmetic talc products. As early as 1968, Cralley et al. Concluded:

> All of the 22 talcum products analyzed have a ...fiber content...averaging 19%. The fibrous material was predominantly talc but probably contained minor amounts of tremolite, anthophyllite, and chrysotile [asbestos-like fibers] as these are often present in fibrous talc mineral deposits...Unknown significant amounts of such materials in products that may be used without precautions may create an unsuspected problem. (9)

As a follow-up to previous findings, Rohl, et al., examined 21 samples of consumer talcums and powders, including baby powders, body powders, facial powders and pharmaceutical powders between 1971-1975. The study concluded:

> ...cosmetic grade talc was not used exclusively. The presence in these products of asbestiform anthophyllite and tremolite, chrysotile, and quartz indicates the need for a regulatory standard for cosmetic talc...We also recommend that evaluation be made to determine the possible health hazards associated with the use of these products.(11,10)

Talc is a carcinogen, with or without the presence of asbestos-like fibers. In 1993, the National Toxicology Program published a study on the toxicity of non-asbestiform talc and found clear evidence of carcinogenic activity (11).

Recent cancer research in the United States has found conclusively that frequent talcum powder application in the genital area increases a woman's risk of developing ovarian cancer (12,13,14,15).

Cramer, et al, suggested that talc application directly to the genital area around the time of ovulation might lead to talc particles becoming deeply imbedded in the substance of the ovary and perhaps causing foreign body reaction (granulomas) capable of causing growth of epithelial ovarian tissue (16,17).

Harlow, et al, found that frequent talc use directly on the genital area during ovulation increased a woman's risk **threefold** . That study also found:

> "The most frequent method of talc exposure was use as a dusting powder directly to the perineum (genitals) . . . Brand or generic 'baby powder' was used most frequently and was the category associated with a statistically significant risk for ovarian cancer."

In Harlow's report, arguably the most comprehensive study of talc use and ovarian cancer to date, 235 ovarian cancer cases were identified and compared to 239 controls, women with no sign of ovarian cancer or

related health problems. Through personal interviews, Harlow, et al, found that 16.7% of the control group reported frequent talc application to the perineum (18). This percentage is useful in estimating the number of women in the general population exposed to cosmetic talc in the genital area on a regular basis. Harlow, et al, concludes:

> ". . . given the poor prognosis for ovarian cancer, any potentially harmful exposures should be avoided, particularly those with limited benefits. For this reason, we discourage the use of talc in genital hygiene, particularly as a daily habit."

Clearly, large numbers of women—an estimated 17%—are using cosmetic talc in the genital area and may not be adequately warned of the risk of ovarian cancer from daily use.

C. CLAIM FOR CATEGORICAL EXCLUSION

A claim for categorical exclusion is asserted pursuant to 21 CFR 25.24 (a) (11).

D. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

This petition is submitted by:
Jill A. Cashen
Samuel S. Epstein, M.D.
Cancer Prevention Coalition

Michael E. Deutsch, Legal Director
Center for Constitutional Rights

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APPENDIX I: Results for an informal survey of talc products in Chicago drug stores.

BABY POWDERS
Johnson & Johnson Baby Powder. Contains: TALC, fragrance.

Osco Brand Baby Powder. Contains: TALC, fragrance.

Jean Nate Perfumed Talc. Contains: TALC, kaolin, magnesium carbonate, fragrance.

Shower to Shower. Contains: TALC, cornstarch, sodium bicarbonate, fragrance, polysaccarides.

Ammens Medicated Powder. Contains: Zinc oxide, cornstarch, fragrance, isostearic acid, PPG-20, methyl glucose ether, TALC.

Cashmere Bouquet Perfumed Powder. Contains: TALC, magnesium carbonate, zinc stearate, fragrance.

Gold Bond Medicated Powder. Contains: Menthol, zinc oxide, boric acid, eucalyptol, methyl salicylate, salicylic acid, TALC, thymol, zinc stearate.

FEMININE PRODUCTS
Vagisil Feminine Powder. Contains: Cornstarch, aloe, mineral oil, magnesium stearate, silica, benzethonium chloride, fragrance.

Vaginex Feminine Powder. Contains: Zinc oxide, cornstarch, fragrance, 6-hydroxquinoline, 8-hydroxquinoline sulfate, isostearic acid, PPG-20, methyl glucose ether, TALC.

Summer's Eve Feminine Powder. Contains: Cornstarch, tricalcium phosphate, oxoxynol-9, benzethonium chloride, fragrance.

FDS Feminine Deodorant Spray. Contains: Isobutane, isopropyl myristate, cornstarch, mineral oil, fragrance, lanolin alcohol, hydrated

silica, magnesium stearate, benzyl alcohol.

Cancer Prevention Coalition

UIC SCHOOL OF PUBLIC HEALTH, MC 922 · 2121 W. TAYLOR ST. · CHICAGO, IL 60612 · (312) 996-2297 · epstein@uic.edu

Cancer prevention through reduction of carcinogens in air, water, food, consumer products, and the workplace

www.preventcancer.com

PETITION SEEKING A CANCER WARNING ON COSMETIC TALC PRODUCTS

May 13, 2008

Mike Leavitt
Secretary of Health and Human Services
U.S. Department of Health and Human Services

Andrew C. von Eschenbach, M.D.
Commissioner of Food and Drugs

Dockets Management Branch
Food and Drug Administration, Room 1601
5630 Fishers Lane
Rockville, MD 20852

Citizen Petition

The undersigned submits this May 13, 2008, Citizen Petition on behalf of: Samuel S. Epstein, M.D., Chairman, Cancer Prevention Coalition (CPC), and Professor emeritus Occupational and Environmental Medicine, University of Illinois at Chicago School of Public Health; Peter Orris, M.D., Professor and Chief of Service, University of Illinois at Chicago Medical Center; Quentin Young, M.D., Chairman, Health and Medicine Policy Research Group, Chicago; Rosalie Bertell, Ph.D., International Association for Humanitarian Medicine, Scientific Advisor to the International Institute of Concern for Public Health, Toronto, and the International Science Oversight Board of the Organic Consumers Association, Washington, D.C.; and Ronnie Cummins, National Director of the Organic Consumers Association.

This Petition, submitted under 21 U.S.C. 321 (n), 361, 362, and 371 (a); and 21 CFR 740.1, 740.2 of 21 CFR 10.30 of the Federal Food, Drug and Cosmetic Act, requests the Commissioner of Food and Drugs to require that all cosmetic talc products bear labels with a warning such as, "Frequent application of talcum powder in the female genital area substantially increases the risk of ovarian cancer."

FDA-2008-P-0309 CP

A. AGENCY ACTION REQUESTED

This Petition requests FDA to take the following action:

(1) Immediately require cosmetic talcum powder products to bear labels with a prominent warning such as: "Frequent talc application in the female genital area is responsible for major risks of ovarian cancer."

(2) Pursuant to 21 CFR 10.30 (h) (2), a hearing which will be held at which time we can present scientific evidence in support of this Petition.

B. STATEMENT OF GROUNDS

On November 17, 1994, the Cancer Prevention Coalition and the New York Center for Constitutional Rights submitted a Citizen Petition to the Commissioner of the FDA, "Seeking Carcinogenic Labeling on all Cosmetic Talc Products." The Petition was endorsed by Quentin Young, M.D., Chairman of The Health and Medicine Policy Research Group, Peter Orris, M.D., Director of Health Hazard Evaluation, Cook County Hospital, and Professor of Medicine, University of Illinois Medical School, Chicago, Nancy Nelson, Chair of the Ovarian Cancer Early Detection and Prevention Foundation, and subsequently by Senator Edward Kennedy. In a 1997 statement to the Senate, he requested the FDA to place a cancer warning on the label of talc products, besides other products containing known carcinogens. However, over a decade later his warning remains ignored.

The 1994 Petition was supported by 15 scientific publications. These included nine, from 1983 to 1992, on the major risks of ovarian cancer from the frequent application of brand or generic talc "baby powder" to the genital area of women without any warning of the risks involved. Two of these publications also reported that the genital application of talc could result in its translocation to the ovary.

The scientific basis of the 1994 Petition was further supported by J. Mande, Acting Associate Commissioner for Legislative Affairs of the Department of Health and Human Services. On August 25, 1993, he admitted that "We are aware that there have been reports in the medical literature between frequent direct female perineal talc dusting over a protracted period of years, and an incremental increase in the statistical odds of subsequent development of certain ovarian cancers . . . (However) at the present time, the FDA is not considering to ban, restrict or require a warning statement on the label of talc containing products."

The scientific basis of the 1994 Petition was also admitted by the industry. In an August 12, 1982, article in the *New York Times*, Johnson & Johnson, the manufacturer and retailer of talc dusting powder, stated it was aware of a publication which concluded that frequent genital application of talc was responsible for a three-fold increased risk of ovarian cancer. Warnings of these risks were emphasized by the Cancer Prevention Coalition in November 19, 1994, in letters to Mr. Ralph Larsen, CEO of Johnson & Johnson, and Mr. C.R. Walgreen, Chairman and CEO of Walgreens. Johnson & Johnson was urged to substitute cornstarch, a safe organic

carbohydrate, for talcum powder products, and also to label its products with a warning on cancer risks.

In spite of the scientific evidence, and admission by Johnson & Johnson, the Petition was denied by Dr. John Bailey, FDA's Director of the Office of Cosmetics and Colors, on the basis of the "limited availability" (of Agency resources) and on alleged scientific grounds. Dr. Bailey is currently Director of the industry's Personal Care Products Council.

Evidence for the May 2008 Petition is supported by Edward Kavanaugh, President of the industry's Cosmetic Toiletry and Fragrance Association. In 2002, he admitted that talc is "toxic," that it "can reach the human ovaries," and that prior epidemiological investigations concluded that its genital application increased the risk of ovarian cancer. Further evidence for this Petition is based on 12 publications since 1995, cited below. These confirm the causal relation between genital application of talc and ovarian cancer, and the protective effect of tubal ligation or hysterectomy, preventing the translocation of talc to the ovary.

As Dr. Andrew C. von Eschenbach, former Director of the National Cancer Institute, is aware, the mortality of ovarian cancer for women over the age of 65, has escalated dramatically since 1975, by 13% for white and 47% for black women (1). There are about 15,300 deaths from ovarian cancer each year. This makes it the fourth most common fatal cancer in women after colon, breast and lung.

A case-control study, the largest to date, confirmed the relation between the perineal use of talc and ovarian cancer (2). This has also been confirmed by other reports (3-7). In view of the strength of this evidence, "formal public health warnings" were urged in 1999 (8). An analysis of 16 pooled studies confirmed a statistically significant 33% increased risk of ovarian cancer associated with the perineal use of talc (9). A report by 19 scientists in eight nations worldwide, under the auspices of the International Agency for Research on Cancer, concluded that eight publications confirmed a 30-60% increased risk of ovarian cancer following the perineal application of talc (10). This risk has been confirmed in other reports (11, 12).

The protective effects of tubal ligation or hysterectomy, preventing the translocation of talc from the perineum to the ovary, have also been confirmed (2, 3, 4, 7).

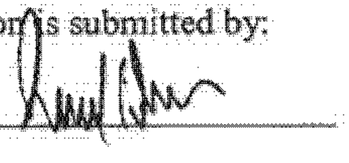
C. CLAIM FOR CATEGORICAL EXCLUSION

A claim for categorical exclusion is asserted pursuant to 21 CFR 25.24 (a) (11).

D. CERTIFICATION

The undersigned certifies, that, to his best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

This petition is submitted by:



Samuel S. Epstein, M.D.
Chairman, Cancer Prevention Coalition
Professor emeritus Occupational and Environmental Medicine
University of Illinois School of Public Health, Chicago

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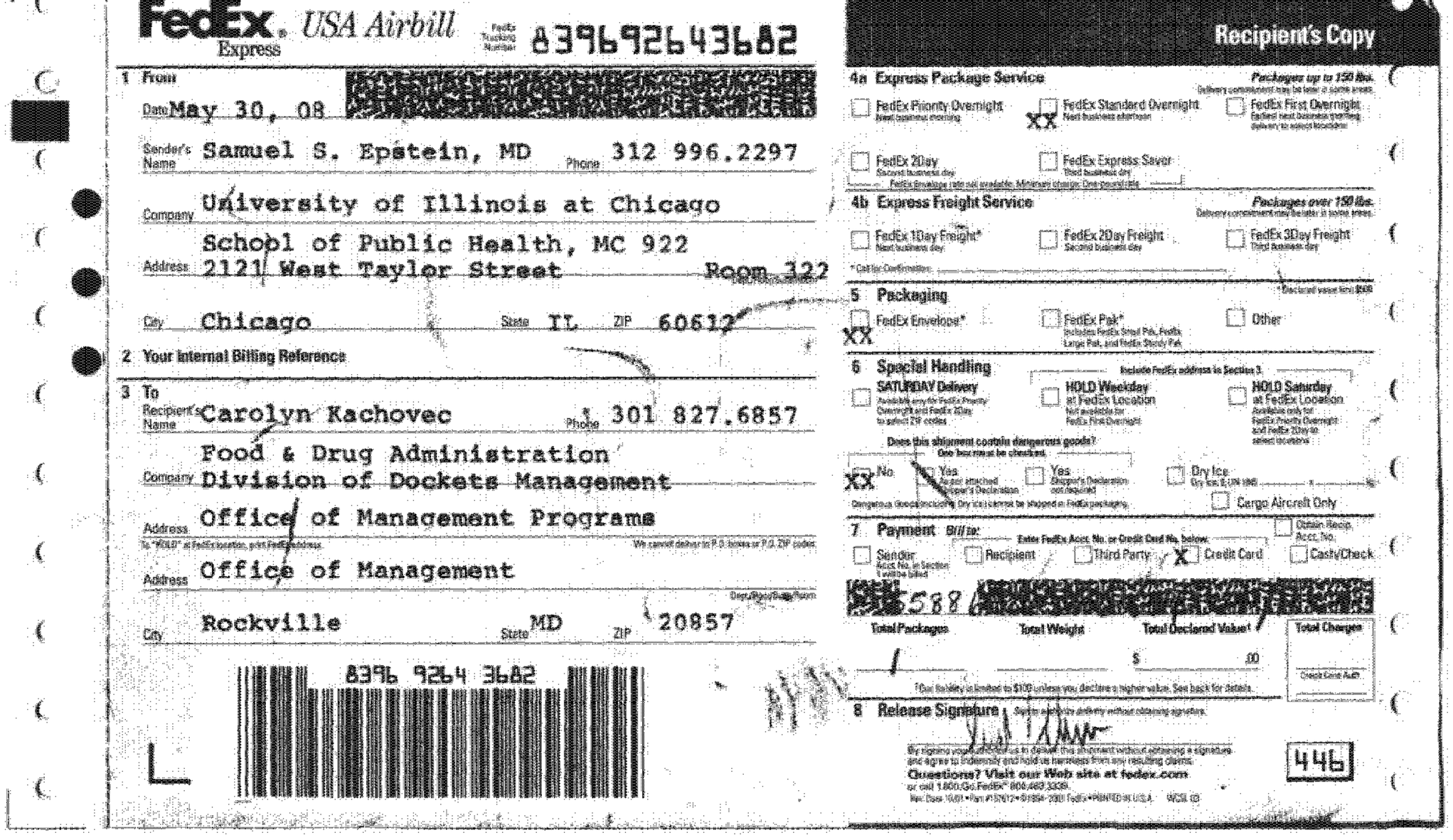

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Response to FDA Request for Information on Talc
Johnson & Johnson Consumer Inc.

Substances Listed in the Thirteenth Report on Carcinogens

Bold entries indicate new or changed listings in the Thirteenth Report on Carcinogens.

Known To Be Human Carcinogens

Aflatoxins
Alcoholic Beverage Consumption
4-Aminobiphenyl
Analgesic Mixtures Containing Phenacetin (see Phenacetin and Analgesic Mixtures Containing Phenacetin)
Aristolochic Acids
Arsenic and Inorganic Arsenic Compounds
Asbestos
Azathioprine
Benzene
Benzidine (see Benzidine and Dyes Metabolized to Benzidine)
Beryllium and Beryllium Compounds
Bis(chloromethyl) Ether and Technical-Grade Chloromethyl Methyl Ether
1,3-Butadiene
1,4-Butanediol Dimethanesulfonate
Cadmium and Cadmium Compounds
Chlorambucil
1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (see Nitrosourea Chemotherapeutic Agents)
Chromium Hexavalent Compounds
Coal Tars and Coal-Tar Pitches
Coke-Oven Emissions
Cyclophosphamide
Cyclosporin A
Diethylstilbestrol
Dyes Metabolized to Benzidine (Benzidine Dye Class) (see Benzidine and Dyes Metabolized to Benzidine)
Erionite
Estrogens, Steroidal
Ethylene Oxide
Formaldehyde
Hepatitis B Virus
Hepatitis C Virus
Human Papillomaviruses: Some Genital-Mucosal Types
Melphalan
Methoxsalen with Ultraviolet A Therapy
Mineral Oils: Untreated and Mildly Treated
Mustard Gas
2-Naphthylamine
Neutrons (see Ionizing Radiation)
Nickel Compounds (see Nickel Compounds and Metallic Nickel)
Radon (see Ionizing Radiation)
Silica, Crystalline (Respirable Size)
Solar Radiation (see Ultraviolet Radiation Related Exposures)
Soots
Strong Inorganic Acid Mists Containing Sulfuric Acid
Sunlamps or Sunbeds, Exposure to (see Ultraviolet Radiation Related Exposures)
Tamoxifen
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
Thiotepa
Thorium Dioxide (see Ionizing Radiation)

Tobacco Smoke, Environmental (see Tobacco-Related Exposures)
Tobacco Smoking (see Tobacco-Related Exposures)
Tobacco, Smokeless (see Tobacco-Related Exposures)
***o*-Toluidine**
Ultraviolet Radiation, Broad-Spectrum (see Ultraviolet Radiation Related Exposures)
Vinyl Chloride (see Vinyl Halides [selected])
Wood Dust
X-Radiation and Gamma Radiation (see Ionizing Radiation)

Reasonably Anticipated To Be Human Carcinogens

Acetaldehyde
2-Acetylaminofluorene
Acrylamide
Acrylonitrile
Adriamycin
2-Aminoanthraquinone
o-Aminoazotoluene
1-Amino-2,4-dibromoanthraquinone
2-Amino-3,4-dimethylimidazo[4,5-*f*]quinoline (see Heterocyclic Amines [Selected])
2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (see Heterocyclic Amines [Selected])
1-Amino-2-methylanthraquinone
2-Amino-3-methylimidazo[4,5-*f*]quinoline (see Heterocyclic Amines [Selected])
2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (see Heterocyclic Amines [Selected])
Amitrole
o-Anisidine and Its Hydrochloride
Azacitidine
Basic Red 9 Monohydrochloride
Benz[*a*]anthracene (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
Benzo[*b*]fluoranthene (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
Benzo[*j*]fluoranthene (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
Benzo[*k*]fluoranthene (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
Benzo[*a*]pyrene (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
Benzotrichloride
2,2-Bis(bromomethyl)-1,3-propanediol (Technical Grade)
Bis(chloroethyl) Nitrosourea (see Nitrosourea Chemotherapeutic Agents)
Bromodichloromethane
1-Bromopropane
Butylated Hydroxyanisole
Captafol
Carbon Tetrachloride
Ceramic Fibers (Respirable Size)
Chloramphenicol
Chlorendic Acid
Chlorinated Paraffins (C_{12}, 60% Chlorine)
Chloroform
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (see Nitrosourea Chemotherapeutic Agents)
3-Chloro-2-methylpropene
4-Chloro-*o*-phenylenediamine
Chloroprene
p-Chloro-*o*-toluidine and Its Hydrochloride
Chlorozotocin (see Nitrosourea Chemotherapeutic Agents)
Cisplatin
Cobalt Sulfate

Cobalt–Tungsten Carbide: Powders and Hard Metals
p-Cresidine
Cumene
Cupferron
Dacarbazine
Danthron
2,4-Diaminoanisole Sulfate
2,4-Diaminotoluene
Diazoaminobenzene
Dibenz[*a,h*]acridine (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
Dibenz[*a,j*]acridine (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
Dibenz[*a,h*]anthracene (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
7H-Dibenzo[*c,g*]carbazole (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
Dibenzo[*a,e*]pyrene (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
Dibenzo[*a,h*]pyrene (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
Dibenzo[*a,i*]pyrene (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
Dibenzo[*a,l*]pyrene (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
1,2-Dibromo-3-chloropropane
1,2-Dibromoethane
2,3-Dibromo-1-propanol
1,4-Dichlorobenzene
3,3′-Dichlorobenzidine and Its Dihydrochloride
Dichlorodiphenyltrichloroethane
1,2-Dichloroethane
Dichloromethane
1,3-Dichloropropene (Technical Grade)
Diepoxybutane
Diesel Exhaust Particulates
Di(2-ethylhexyl) Phthalate
Diethyl Sulfate
Diglycidyl Resorcinol Ether
3,3′-Dimethoxybenzidine (see 3,3′-Dimethoxybenzidine and Dyes Metabolized to 3,3′-Dimethoxybenzidine)
4-Dimethylaminoazobenzene
3,3′-Dimethylbenzidine (see 3,3′-Dimethylbenzidine and Dyes Metabolized to 3,3′-Dimethylbenzidine)
Dimethylcarbamoyl Chloride
1,1-Dimethylhydrazine
Dimethyl Sulfate
Dimethylvinyl Chloride
1,6-Dinitropyrene (see Nitroarenes [Selected])
1,8-Dinitropyrene (see Nitroarenes [Selected])
1,4-Dioxane
Disperse Blue 1
Dyes Metabolized to 3,3′-Dimethoxybenzidine (3,3′-Dimethoxybenzidine Dye Class)
(see 3,3′-Dimethoxybenzidine and Dyes Metabolized to 3,3′-Dimethoxybenzidine)
Dyes Metabolized to 3,3′-Dimethylbenzidine (3,3′-Dimethylbenzidine Dye Class)
(see 3,3′-Dimethylbenzidine and Dyes Metabolized to 3,3′-Dimethylbenzidine)
Epichlorohydrin
Ethylene Thiourea
Ethyl Methanesulfonate
Furan
Glass Wool Fibers (Inhalable), Certain
Glycidol
Hexachlorobenzene

Hexachloroethane
Hexamethylphosphoramide
Hydrazine and Hydrazine Sulfate
Hydrazobenzene
Indeno[1,2,3-*cd*]pyrene (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
Iron Dextran Complex
Isoprene
Kepone
Lead and Lead Compounds
Lindane, Hexachlorocyclohexane (Technical Grade), and Other Hexachlorocyclohexane Isomers
2-Methylaziridine
5-Methylchrysene (see Polycyclic Aromatic Hydrocarbons: 15 Listings)
4,4′-Methylenebis(2-chloroaniline)
4,4′-Methylenebis(*N*,*N*-dimethyl)benzenamine
4,4′-Methylenedianiline and Its Dihydrochloride
Methyleugenol
Methyl Methanesulfonate
N-Methyl-*N*′-Nitro-*N*-Nitrosoguanidine (see *N*-Nitrosamines: 15 Listings)
Metronidazole
Michler's Ketone
Mirex
Naphthalene
Nickel, Metallic (see Nickel Compounds and Metallic Nickel)
Nitrilotriacetic Acid
o-Nitroanisole
Nitrobenzene
6-Nitrochrysene (see Nitroarenes [Selected])
Nitrofen
Nitrogen Mustard Hydrochloride
Nitromethane
2-Nitropropane
1-Nitropyrene (see Nitroarenes [Selected])
4-Nitropyrene (see Nitroarenes [Selected])
N-Nitrosodi-*n*-butylamine (see *N*-Nitrosamines: 15 Listings)
N-Nitrosodiethanolamine (see *N*-Nitrosamines: 15 Listings)
N-Nitrosodiethylamine (see *N*-Nitrosamines: 15 Listings)
N-Nitrosodimethylamine (see *N*-Nitrosamines: 15 Listings)
N-Nitrosodi-*n*-propylamine (see *N*-Nitrosamines: 15 Listings)
N-Nitroso-*N*-ethylurea (see *N*-Nitrosamines: 15 Listings)
4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (see *N*-Nitrosamines: 15 Listings)
N-Nitroso-*N*-methylurea (see *N*-Nitrosamines: 15 Listings)
N-Nitrosomethylvinylamine (see *N*-Nitrosamines: 15 Listings)
N-Nitrosomorpholine (see *N*-Nitrosamines: 15 Listings)
N-Nitrosonornicotine (see *N*-Nitrosamines: 15 Listings)
N-Nitrosopiperidine (see *N*-Nitrosamines: 15 Listings)
N-Nitrosopyrrolidine (see *N*-Nitrosamines: 15 Listings)
N-Nitrososarcosine (see *N*-Nitrosamines: 15 Listings)
o-Nitrotoluene
Norethisterone
Ochratoxin A
4,4′-Oxydianiline
Oxymetholone
Pentachlorophenol and By-products of Its Synthesis

Phenacetin (see Phenacetin and Analgesic Mixtures Containing Phenacetin)
Phenazopyridine Hydrochloride
Phenolphthalein
Phenoxybenzamine Hydrochloride
Phenytoin and Phenytoin Sodium
Polybrominated Biphenyls
Polychlorinated Biphenyls
Procarbazine and Its Hydrochloride
Progesterone
1,3-Propane Sultone
β-Propiolactone
Propylene Oxide
Propylthiouracil
Reserpine
Riddelliine
Safrole
Selenium Sulfide
Streptozotocin (see Nitrosourea Chemotherapeutic Agents)
Styrene
Styrene-7,8-oxide
Sulfallate
Tetrachloroethylene
Tetrafluoroethylene
Tetranitromethane
Thioacetamide
4,4′-Thiodianiline
Thiourea
Toluene Diisocyanates
Toxaphene
Trichloroethylene
2,4,6-Trichlorophenol
1,2,3-Trichloropropane
Tris(2,3-dibromopropyl) Phosphate
Ultraviolet Radiation A (see Ultraviolet Radiation Related Exposures)
Ultraviolet Radiation B (see Ultraviolet Radiation Related Exposures)
Ultraviolet Radiation C (see Ultraviolet Radiation Related Exposures)
Urethane
Vinyl Bromide (see Vinyl Halides [Selected])
4-Vinyl-1-cyclohexene Diepoxide
Vinyl Fluoride (see Vinyl Halides [Selected])

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Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention–Health Professional Version (PDQ®)

Description of the Evidence

Background

Incidence and mortality

In 2016, it is estimated that 22,280 new cases of ovarian cancer will be diagnosed and 14,240 deaths due to ovarian cancer will occur.[1] Incidence and mortality rates are higher among whites than among blacks, but statistically significant decreases in incidence and mortality rates have been observed among both whites and blacks.[2] A statistically significant decrease in delayed adjusted incidence of 0.9% among whites from 1987 to 2012 and 0.2% among blacks from 1992 to 2012 has been observed. A statistically significant decrease in mortality rates of 2.0% per year among whites from 2002 to 2012 and 1.3% per year among blacks from 1992 to 2012 has been observed. The population lifetime risk of ovarian cancer is 1.3%; the population lifetime risk of dying from ovarian cancer is 0.97%.[2]

Histology and Pathogenesis of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

Ovarian cancer may be of germ cell, stromal, or epithelial origin.[3] Epithelial ovarian cancer, the most common type, is the focus of this summary. The term epithelial ovarian cancer encompasses a heterogeneous group of tumors. Classically, ovarian tumors have been classified as serous, mucinous, endometrioid, and clear cell. However, a dual classification system of type I and type II tumors has been proposed that incorporates molecular profiling of tumors as well as histology and clinical behavior.[4] Type I tumors usually present at a low stage, are associated with an excellent clinical prognosis, and encompass borderline malignant tumors. Type II tumors are more aggressive, usually present in an advanced stage, and have a variety of histologies. Type I tumors tend to be more stable genetically than type II tumors, with type II tumors also having a high prevalence of *TP53* mutations. About 75% of epithelial cancers are type II tumors and include ovarian cancer such as serous, endometrioid, and mixed mesodermal tumors. There is increasing evidence that the two types of cancers are different genetically, and thus, may have different molecular pathways of development. Evidence also suggests that both of these types develop outside the ovary and then secondarily involve the ovary, with most type II tumors being of tubal origin.[4] This is hypothesized to be the case for both genetic cancers (*BRCA1/2*-mutation associated cancers) and most noninherited forms of ovarian cancer.

The heterogeneity of ovarian cancer and the suggestion of different molecular pathways of origin for cancer subtypes present challenges and opportunities for the conduct and interpretation of etiologic factors associated with the development of ovarian cancer. Etiologic association may vary by the mix of subtypes in the populations included in the epidemiologic studies. Ovarian cancer is a rare cancer, thus sample size and power of studies to detect moderate association by subtype of cancer are limited. However, clearer subtyping of cancers may assist is improving our understanding of the etiology of ovarian malignancies in future studies.

Inherited Susceptibility to Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

Some women are at an increased risk because of an inherited susceptibility to ovarian cancer, with the magnitude of that

risk depending on the affected gene and specific mutation. Underlying ovarian cancer risk can be assessed through accurate pedigrees and/or genetic markers of risk. Because of uncertainties about cancer risks associated with specific gene mutations, genetic information may be difficult to interpret outside of families with a high incidence of ovarian cancer. The following three inherited ovarian cancer susceptibility syndromes have been described: (1) familial site-specific ovarian cancer; (2) familial breast/ovarian cancer; and (3) Lynch II syndrome, which is a combination of breast, ovarian, endometrial, gastrointestinal, and genitourinary cancers.[5,6] Considering family history in the absence of specific information on *BRCA1/2* mutation status, unaffected women who have two or three relatives with ovarian cancer have a cumulative ovarian cancer risk of about 7%.[5,7] Women who have a mother or sister with ovarian cancer have a cumulative lifetime risk of ovarian cancer of about 5%.

Multiple genetic syndromes are not addressed in this summary. This summary also does not address women who are at high risk because of inherited genetic factors. (Refer to the PDQ summaries on Genetics of Breast and Gynecologic Cancers and Genetics of Colorectal Cancer for specific information related to ovarian cancer risk associated with multiple genetic syndromes and ovarian cancer in *BRCA1/2* mutation carriers.)

Factors With Adequate Evidence of an Increased Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

Hormone replacement therapy/hormone therapy

A modest association between current, but not past, postmenopausal hormone therapy use and incident ovarian cancer was observed in the Million Women Study.[8] The Million Women Study reported on 2,273 incident cases of ovarian cancer observed among women followed for an average of 5.3 years. The relative risk (RR) among current users of hormone therapy compared with women who never used hormone therapy was 1.20 (95% confidence interval [CI], 1.09–1.32). A dose-response relationship was observed with increasing risk, noted with increasing duration of use. The observed RRs were higher for estrogen-only therapy than for combined estrogen-progestogen therapy (RR, 1.34; 95% CI, 1.13–1.60 vs. RR, 1.14; 95% CI, 1.01–1.28, respectively). No excess risk of ovarian cancer was observed among past users.

As in the Million Women Study, a population-based case-control study conducted in Washington State observed an association between ovarian cancer and current or recent use (within the last 3 years) of exclusively estrogen-only therapy for at least 5 years (current use: odds ratio [OR], 1.6; 95% CI, 1.1–2.5; recent use: OR, 1.8; 95% CI, 0.8–3.7). However, no increased risk was observed among users of combined estrogen-progestogen therapy.[9]

The Women's Health Initiative estrogen-progestin randomized trial observed a nonstatistically significant excess risk of ovarian cancer, based on 32 cases of ovarian cancer at the 5.6-year follow-up (hazard ratio, 1.58; 95% CI, 0.77–3.24).[10] An accelerated decline in ovarian cancer incidence rates after 2002—following the report of the Women's Health Initiative and subsequent decline in the use of hormone therapy—supports, but does not prove, a causal association between hormone therapy and ovarian cancer risk.[11]

Obesity and height

Obesity is associated with increased mortality from ovarian cancer.[12] In cohort studies, height and body mass index (BMI),[13,14] including high BMI during adolescence,[14] were associated with an increased risk of ovarian cancer, suggesting a role for diet and nutrition during the adolescent period.

Factors With Adequate Evidence of a Decreased Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

Oral contraceptives

A collaborative analysis was performed of individual data from 23,257 women with ovarian cancer and 87,303 women without ovarian cancer from 45 studies in 21 countries.[15] The studies included 13 prospective studies, 19 population-

based case-control studies, and 12 hospital-based case-control studies. Oral contraceptive use was associated with a dose-response effect by duration of use, with no observed changes in risk reduction by decade of use from the 1960s to 1980s, over which time the amount of estrogen in oral contraceptives was approximately halved. No risk reduction was observed for women who used oral contraceptives for less than 1 year. The risk reduction associated with use from 1 to 4 years, 5 to 9 years, 10 to 14 years, and 15 years or more was 0.78 (99% CI, 0.73–0.893), 0.64 (99% CI, 0.59–0.69), 0.56 (99% CI, 0.50–0.62), and 0.42 (99% CI, 0.36–0.49), respectively. The observed risk reduction persisted after cessation of oral contraceptive therapy but attenuated over time since last use. The proportional reduction in risk per 5 years of use was 29% (95% CI, 23%–34%) for women who had discontinued use within the last 10 years; the reduction in risk was 15% (95% CI, 9%–21%) for women who discontinued use 20 to 29 years ago.

A meta-analysis that was restricted to 24 case-control and cohort studies published since 2000 for the primary analysis—in order to reflect more recent types of oral contraceptive preparations—also observed a dose-response by duration of use.[16] The risk reduction among women using oral contraceptives for more than 1 year but less than 5 years was 0.77 (95% CI, 0.66–0.89), and for women using oral contraceptives for more than 10 years, the risk reduction was 0.43 (95% CI, 0.37–0.51). The authors estimated that 185 women needed to be treated for 5 years to prevent one case of ovarian cancer. Based on an estimated lifetime risk of 1.38% and prevalence of ever-use of oral contraceptives of 83%, the authors estimated a lifetime reduction of ovarian cancer attributable to oral contraceptives of 0.54%.

(Refer to the PDQ summary on Genetics of Breast and Gynecologic Cancers for specific information related to ovarian cancer risk among *BRCA1/2* mutation carriers.)

Depot-medroxyprogesterone acetate

Limited information is available on the use of injectable progestational contraceptives (depot-medroxyprogesterone acetate [DMPA]) and the risk of ovarian cancer; studies are confounded by the use of other contraceptive methods, particularly oral contraceptives. A hospital-based study conducted in Mexico and Thailand, with 224 cases and 1,781 controls (the World Health Organization collaborative study of neoplasia and steroid contraceptives), observed no association between DMPA and ovarian cancer (RR, 1.07; 95% CI, 0.6–1.8).[17] However, only 22 of the cases had ever used DMPA and nine of these had used it for 6 months or less.

A subsequent multicenter study conducted in 12 hospitals in Thailand, including 330 cases and 982 matched controls, observed a statistically significant decreased risk of ovarian cancer associated with DMPA use, controlling for oral contraceptive use and other associated factors (OR, 0.52; 95% CI, 0.33–0.88). A dose-response association was observed but the sample size was limited in longer-term use categories.[18]

Tubal ligation

A meta-analysis of 16 case-control studies, three retrospective studies, and two prospective cohort studies observed a decreased risk of ovarian cancer associated with tubal ligation (RR, 0.66; 95% CI, 0.60–0.73).[19] The reduced risk was observed up to 14 years after tubal ligation. A population-based case-control study of 902 cases and 1,802 controls published subsequent to the meta-analysis observed an adjusted OR of 0.62 (95% CI, 0.51–0.75) associated with a history of a tubal ligation.[20] The association was adjusted for oral contraceptive use, which was also associated with a lower risk of ovarian cancer (OR, 0.62; 95% CI, 0.47–0.85) and other risk factors.[20]

Another pooling project with primary data from 13 population-based case-control studies examined the association between tubal ligation and ovarian cancer risk and included 7,942 epithelial ovarian cancers, 2,215 borderline tumors, and 13,904 controls.[21] Overall, tubal ligation was associated with a 29% reduction in risk (OR, 0.71; 95% CI, 0.66–0.77). The observed risk reduction varied by subtype of invasive cancers and was 52% (OR, 0.48; 95% CI, 0.40–49) for endometrioid cancer; 48% (OR, 0.52; 95% CI, 0.40–0.67) for clear cell cancer; 32% (OR, 0.68; 95% CI, 0.52–89) for mucinous cancer; and 19% (OR, 0.81; 95% CI, 0.74–0,89) for serous cancer. No significant association was observed between tubal ligation and risk of borderline ovarian tumors.

The United States Collaborative Review of Sterilization includes data from 15 participating institutions collected from nine

cities from 1978 to 1987.[22] The rate of unintended major surgery was 0.9 per 100 procedures. Other reported complications included rehospitalization (0.6 per 100 procedures), febrile morbidity (0.1 per 100 procedures), and transfusion (<0.01 per 100 procedures). No deaths were reported among 9,475 women who had laparoscopic surgery. One life-threatening event of anaphylaxis, presumed to be caused by anesthesia, was reported. Overall rates did not statistically significantly vary by type of methods (silicone rubber band application, spring clip, or unipolar or bipolar coagulation).

Breast-feeding

A meta-analysis [23] that included five prospective studies and 30 case-control studies examined the association between breast-feeding and the risk of ovarian cancer. Any breast-feeding was associated with a decreased risk of ovarian cancer (RR, 0.76; 95% CI, 0.69–0.83). The risk of ovarian cancer decreased 8% for every 5-month increase in duration of breast-feeding (95% CI, 0.90–0.95).

Risk-reducing salpingo-oophorectomy

Risk-reducing surgery is an option considered by women who are at high risk of ovarian cancer, such as those with an inherited susceptibility to cancer. (Refer to the Oral contraceptives section in the PDQ summary on Genetics of Breast and Gynecologic Cancers for more information on this as a risk-reducing intervention.)

Factors With Inadequate Evidence of an Association

Dietary factors

No consistent association has been observed between a variety of dietary factors and the risk of ovarian cancer.

A systematic review and meta-analysis that included 23 case-control studies and three cohort studies found no evidence of an association between alcohol use and epithelial ovarian cancer.[24]

A case-control study of the Healthy Eating Index (HEI), based on current U.S. Department of Agriculture dietary guidelines, found no association between the highest HEI score and ovarian cancer risk for any specific food group.[25] A systematic review of the role of diet in ovarian cancer included only prospective studies, with at least 200 reported cases in the publications.[26] Twenty-four publications from ten cohort studies were reviewed and no dietary factors were consistently associated with the risk of ovarian cancer. Tea consumption was not specifically addressed in that review, but another systematic review included 16 articles, with nine articles reporting no association with tea consumption, five reporting a decreased risk, and one each reporting a borderline decreased and increased risk associated with tea consumption.[27] A case-control study conducted in southern China (500 cases and 500 controls), published subsequent to the review, reported a protective association between regular drinking of green tea, black tea, and/or oolong tea, with an OR of 0.29 (95% CI, 0.22–0.39).[28]

Circulating vitamin D levels and the association with ovarian cancer was examined in a nested case-control study (516 cases and 770 matched controls) conducted among seven prospective cohorts.[29] No association was observed between circulating 25-hydroxyvitamin D [25(OH)D] levels and the development of ovarian cancer. A nested case-control study in Finland (172 ovarian cancer cases and 172 matched controls) observed a decreased risk of ovarian cancer among women who had 25(OH)D levels of more than 75 nmol/L (considered sufficient) compared with women who had lower levels (OR, 0.32; 95% CI, 0.12–0.91).[30]

The Australian Ovarian Cancer Study (1,366 cases and 1,414 population controls) [31] found no association between intake of omega-3 fatty acids and ovarian cancer risk. High intake of omega-6 fatty acids that came from avocados, vegetables, or nuts, but not other sources, was associated with a modest decreased risk (OR, 0.78; 95% CI, 0.60–1.00). Overall, the authors concluded that the benefit from omega-6 fatty acids was from the general properties of the food source rather than from the omega-6 fatty acid per se.

Aspirin and nonsteroidal anti-inflammatory drugs

A systematic review and meta-analysis of 21 observational studies found a decreased risk of invasive ovarian cancer associated with aspirin use (RR, 0.88; 95% CI, 0.79–0.98), but no statistically significant association with nonsteroidal anti-inflammatory drugs (NSAIDS).[32] A study published subsequent to that review examined NSAIDs use and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study. No association was observed between the development of ovarian cancer and regular aspirin use (RR, 1.06; 95% CI, 0.87–1.29) or NSAIDS use (RR, 0.93; 95% CI, 0.74–1.15).[33] A population-based case-control study [34] of 902 incident cases and 1,802 population controls observed a decreased risk of ovarian cancer associated with continual use (0.71; 95% CI, 0.53–0.97) or low-dose daily use (0.72; 95% CI, 0.53–0.97). In that study, selective cyclo-oxygenase-2 NSAIDS but not nonselective NSAIDS were associated with a decreased risk of ovarian cancer (OR, 0.60; 95% CI, 0.39–0.94).

Smoking

An individual participant meta-analysis from 51 studies that included 28,114 women with ovarian cancer found a very small increased risk of ovarian cancer among current smokers compared with women who never smoked (RR, 1.06; 95% CI, 1.01–1.11).[35] Smoking risk varied by subtype, with no association observed for serous ovarian cancer (RR, 0.99; 95% CI, 0.93–1.06), an excess risk for mucinous cancers (RR, 1.79; 95% CI, 1.60–2.00), and a decreased risk for endometrioid (RR, 0.81; 95% CI, 0.72–0.92) and clear-cell ovarian cancer (RR, 0.80; 95% CI, 0.65–0.97).

Perineal talc exposure

The evidence is inadequate to determine whether perineal talc exposure is associated with an increased risk of ovarian cancer. Results from case-control and cohort studies are inconsistent. A meta-analysis of 16 studies observed an increased risk with the use of talc (RR, 1.33; 95% CI, 1.16–1.45); however, there was no evidence of a dose response.[36] A pooled analysis from the Ovarian Cancer Association Consortium, composed of multiple case-control studies, included 8,525 cases and 9,859 controls. A modest increased risk of epithelial ovarian cancer associated with genital powder use (OR, 1.24; 95% CI, 1.15–1.33) was observed but the trend across increasing lifetime number of applications was not statistically significant (*P* trend = .17).[37] A cohort study among nurses did not observe a risk of ovarian cancer associated with perineal talc use (RR, 1.09; 95% CI, 0.86–1.37) and there was no evidence of increased risk with increasing frequency of use.[38] Another prospective study, The Women's Health Initiative, examined the association between perineal powder use and the development of ovarian cancer among 61,576 women with no history of cancer at enrollment and who provided exposure information. Among this group, 429 cases of ovarian cancer occurred. Powder use on genitals, sanitary napkins, and diaphragms was examined individually and as a combined exposure. Women were followed for a mean of 12.4 years. No association of ovarian cancer was observed with ever-use of perineal powder compared with never-use when analyzed either by individual method of exposure or by overall combined exposure. The observed risk (hazard ratio) for combined exposure to perineal powder was 1.06 (95% CI, 0.87–1.28) and there was no increased risk observed for increasing duration of use.[39]

Areas of Uncertainty

Ovarian hyperstimulation due to infertility treatment

Controversy persists concerning the association between ovarian hyperstimulation and ovarian cancer. A systematic review and meta-analysis of nine cohort studies comprised 109,969 women who were exposed to ovarian hyperstimulation for infertility treatment (i.e., *in vitro* fertilization [IVF]), with 76 incident ovarian cancer cases observed.[40] An increased risk of ovarian cancer was observed when the comparison group was the general population (RR, 1.50; 95% CI, 1.17–1.92), but no statistically significant increased risk was observed when the reference group was unexposed infertile women (RR, 1.26; 95% CI, 0.62–2.55). A major limitation was that only one of the cohort studies included in the meta-analysis had a follow-up period longer than 10 years for those exposed to IVF.

A Cochrane systematic review included 11 case-control studies and 14 cohort studies, for a total of 186,972 women; however, summary statistics were not calculated because of methodological and clinical heterogeneity. Among seven cohort studies that compared treated women with untreated subfertile women, no excess risk was noted in association

with hyperstimulation medications. Two cohorts noted an increased risk of twofold to fivefold when treated women were compared with the general population. An increased risk of borderline ovarian tumors was noted in three case-control studies and two cohort studies. Overall, the authors concluded there was no convincing evidence that an increased risk of invasive ovarian tumors was associated with fertility drug treatments, but there may be an increased risk of borderline ovarian tumors.[41]

A follow-up study of an infertility cohort [42] was published subsequent to the aforementioned Cochrane review. A retrospective cohort of 9,825 women enrolled between 1965 and 1988 was followed through 2010. Ovarian cancer occurred in 85 women. Overall, there was no association between ovarian cancer and clomiphene citrate (RR, 1.34; 95% CI, 0.86–2.07) or gonadotropins (RR, 1.00; 95% CI, 0.48–2.08). Among the subgroup of women who remained nulligravid after treatment, an increased risk of ovarian cancer was associated with clomiphene citrate (RR, 3.63; 95% CI, 1.36–9.72); no increased risk was observed among women who successfully conceived after being treated, compared with women who were not treated.

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WORLD HEALTH ORGANIZATION
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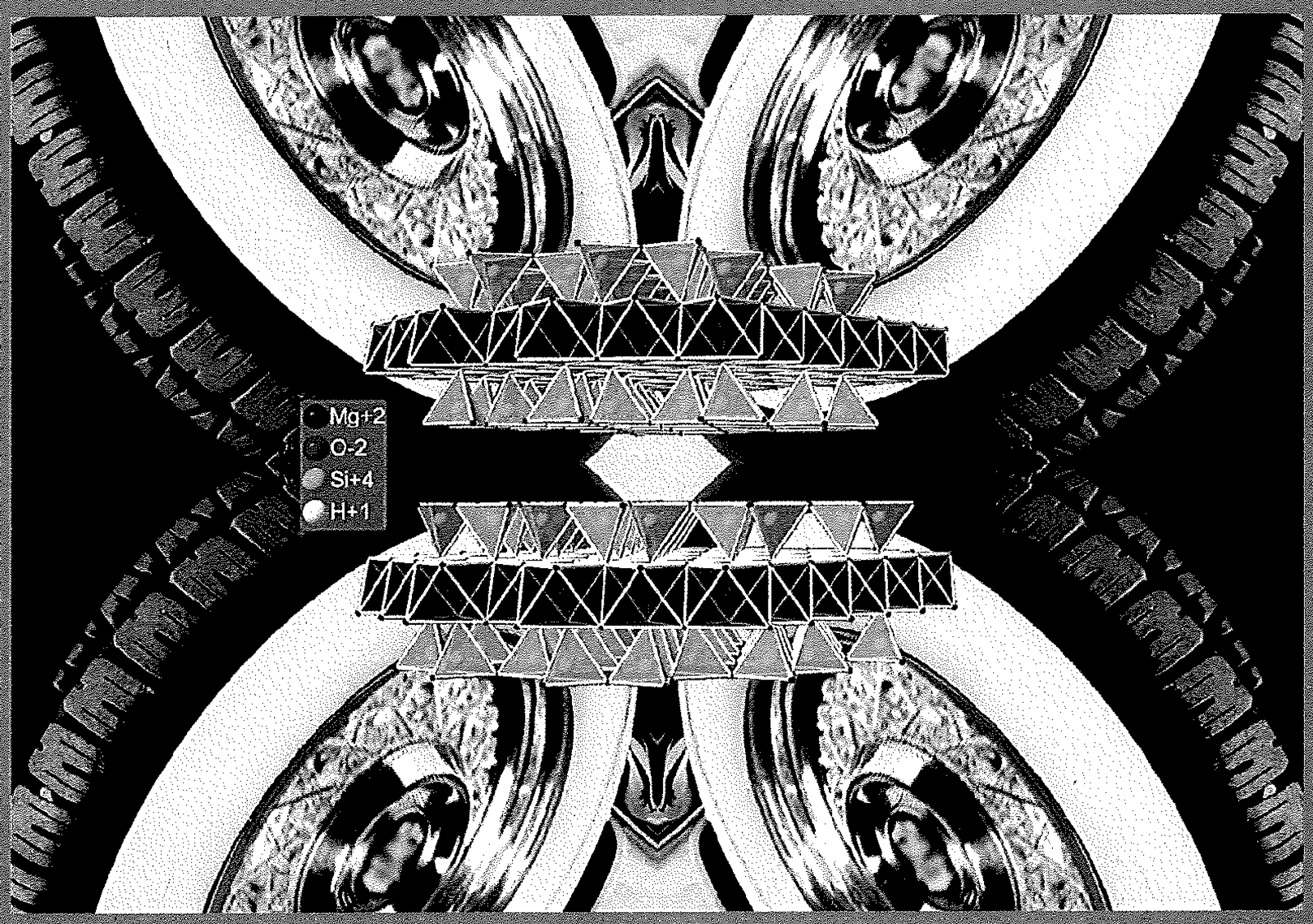
IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 93

Carbon Black, Titanium Dioxide, and Talc



LYON, FRANCE
2010

WORLD HEALTH ORGANIZATION
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IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 93

Carbon Black, Titanium Dioxide, and Talc

This publication represents the views and expert opinions
of an IARC Working Group on the
Evaluation of Carcinogenic Risks to Humans,
which met in Lyon,

7–14 February 2006

2010

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at http://monographs.iarc.fr/.

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CONTENTS

TALC NOT CONTAINING ASBESTIFORM FIBRES

1. Exposure Data

Introduction

Talc refers to both mineral talc and industrial mineral products that are marketed under the name talc and contain proportions of mineral talc that range from about 35% to almost 100%.

The mineralogy of airborne particles in talc mines is restricted by that of the deposit and associated rocks. Therefore, mines and mills provide an opportunity to characterize exposure to one specific source of talc mineralogically. In contrast, the mineralogy of talc in an industrial setting where talc products are used may be difficult to characterize, because many different sources of talc are available for almost every application. Industrial talcs are quite variable in their talc content and in the identity and proportion of other minerals that they contain. In addition, talc is part of a complex mixture of materials in user industries.

Talc particles are normally plate-like. When viewed under the microscope in bulk samples or on air filters, they may appear to be fibres and have been identified as such. Talc may also form as true mineral fibres that are asbestiform; asbestiform describes the pattern of growth of a mineral that is referred to as a 'habit'. Asbestiform talc fibres are very long and thin and occur in parallel bundles that are easily separated from each other by hand pressure.

Asbestos is a commercial term that describes six minerals that occur in the asbestiform habit: actinolite, anthophyllite, chrysotile, grunerite, riebeckite and tremolite (IARC, 1977). Similarly to talc, these six minerals occur more commonly in a non-asbestiform habit, and may also be elongated without being asbestiform. Actinolite, anthophyllite and tremolite may occur in some talc deposits; when asbestiform, they constitute asbestos and, when not asbestiform, they are referred to as mineral fragments or cleavage fragments.

1.1 Chemical and physical data

1.1.1 *Nomenclature*

CAS Registry No.: 14807–96–6
Chem. Abstr. Name: Talc
Synonyms[1]*:* Soapstone; steatite; talcum
Trade names[1]*:* Trade names of industrial, cosmetic and pharmaceutical talc include Agalite, Asbestine, Australian microcrystalline, Beaver White 200, CP 10–40, CP 38–33, Crystalite CR 6002, Desertalc 57, Emtal 500, Emtal 549, Emtal 596, Emtal 599, Ex-IT, Fibrene C 400, Finntalc, French Chalk, FW-XO, HSDB 830, IT Extra, LMR 100, Microneeca K1, Micro White 5000A, Microtalco IT Extra, Mistron, Montana talc, MP 25–38, MP 40–27, MP 45–26, MST, MT 12–50, Mussolinite, NCI-CO6018, Nytal 200, Nytal 400, Pk-C, Pk-N, Plustalc, Polytal 4641, Polytal 4725, Snowgoose, Steawhite, Supreme, Supreme dense, Talcan PK-P, Talcron CP 44–31 and Westmin.

Rocks or mineral composites that contain talc mineral include agalite, potstone, soapstone and talcite. Soapstone generally contains at least 25% of minerals other than talc while talcite is sometimes used to describe rock that contains at least 75% talc (Harben & Kuzvart, 1996). Steatite originally referred to a rock that is relatively pure talc; today, it denotes a ceramic body with a high talc content that is used as an electrical insulator. The talc that is used in such applications is known as steatitic talc. French chalk is soft massive talc (Piniazkiewicz *et al.*, 1994). Talc has also been referred to as snowgoose, agalite and kerolite. Industrial talc generally refers to products that contain abundant minerals other than talc; cosmetic talc now normally contains >98% talc (Zazenski *et al.*, 1995) but the content may have been lower in the past (Rohl *et al.*, 1976). Pharmaceutical talc contains >99% talc. Talcum powder is cosmetic-grade talc (Zazenski *et al.*, 1995). Pyrophyllite is similar to talc in atomic structure but contains aluminium instead of magnesium ($Al_2Si_4O_{10}(OH)_2$) (Bish & Guthrie, 1993); the two minerals do not occur together in nature, although they have similar industrial applications.

1.1.2 *Structure of the typical mineral*

Chemical formula: $Mg_3Si_4O_{10}(OH)_2$
Molecular weight: 379.26

The original X-ray spectra of talc (Gruner, 1934; Hendricks, 1938) indicated that mineral talc had a monoclinic structure. Later investigations (Ross *et al.*, 1968; Rayner & Brown, 1973) demonstrated that talc is triclinic (Table 1.1). The small deviations from 90° in angle α and angle γ result in the triclinic symmetry. Indexing the X-ray diffraction

[1] These synonyms and trade names cover talc, materials that contain talc and talc that is contaminated with other minerals as admixtures.

pattern as a monoclinic structure assumes that angles α and γ are each 90° and doubles the magnitude of one of the lattice parameters (parameter 'c' in Table 1.1).

Table 1.1. Lattice parameters and crystallographic axes of talc

Lattice parameters (nm)			Crystallographic axes			System	References
a	b	c	α	β	γ		
0.5255	0.9137	0.9448	90°46′	98°55′	90°00′	Triclinic	Ross *et al.* (1968)
0.5293	0.9179	0.9496	90°57′	98°91′	90°03′	Triclinic	Rayner & Brown (1973)

The structure of talc is characterized by a hexagonal sheet arrangement of silicon–oxygen tetrahedral groups linked in a common plane. Each silicon–oxygen tetrahedron shares three planar oxygen atoms with its neighbouring tetrahedra; the fourth oxygen, the apex of the tetrahedron, is not shared. Two such sheets are orientated so that unshared apical oxygen atoms face each other. The sheets are bonded by magnesium atoms that are coordinated octahedrally by two oxygen atoms from each tetrahedral sheet and two hydroxyl groups. This structural arrangement results in a double-sheet structure in which the valence demands of the constituent atoms are completely satisfied without interlayer cations; these double-sheet units are held together only by weak van der Waal's bonds. The double-sheet units are easily separated by slight forces that result in a perfect cleavage direction in the basal plane (Rohl *et al.*, 1976; Pooley & Rowlands, 1975). The structure of talc is depicted in Figure 1.1 (see cover photo of this Volume).

1.1.3 *Chemical and physical properties of mineral talc*

Hardness: 1 on Mohs' scale
Density: 2.58–2.83
Cleavage: (001) perfect
Colour: Pale to dark green or greenish grey to black; also white, silvery-white, grey, brownish
Luster: Translucent; pearly, greasy or dull
Indices of refraction: Talc is biaxial with α=1.539–1.550, β=1.589–1.594 and γ=1.589–1.600. The indices of refraction increase with iron content. Because β and γ are approximately equal, talc appears to be uniaxial (Deer *et al.*, 1962).
Description: Commonly thin tabular crystals, up to 1 μm in width; talc is usually massive, fine-grained and compact; it also occurs as foliated or fibrous masses or in globular stellate groups. Talc particles are normally thin and plate-like, but the size of the individual plates varies among different bodies of ore. When viewed under the microscope on end, talc platelets may appear as fibres (Cralley *et al.*, 1968). These are not true fibres and should not be confused with asbestiform talc. Asbestiform talc is

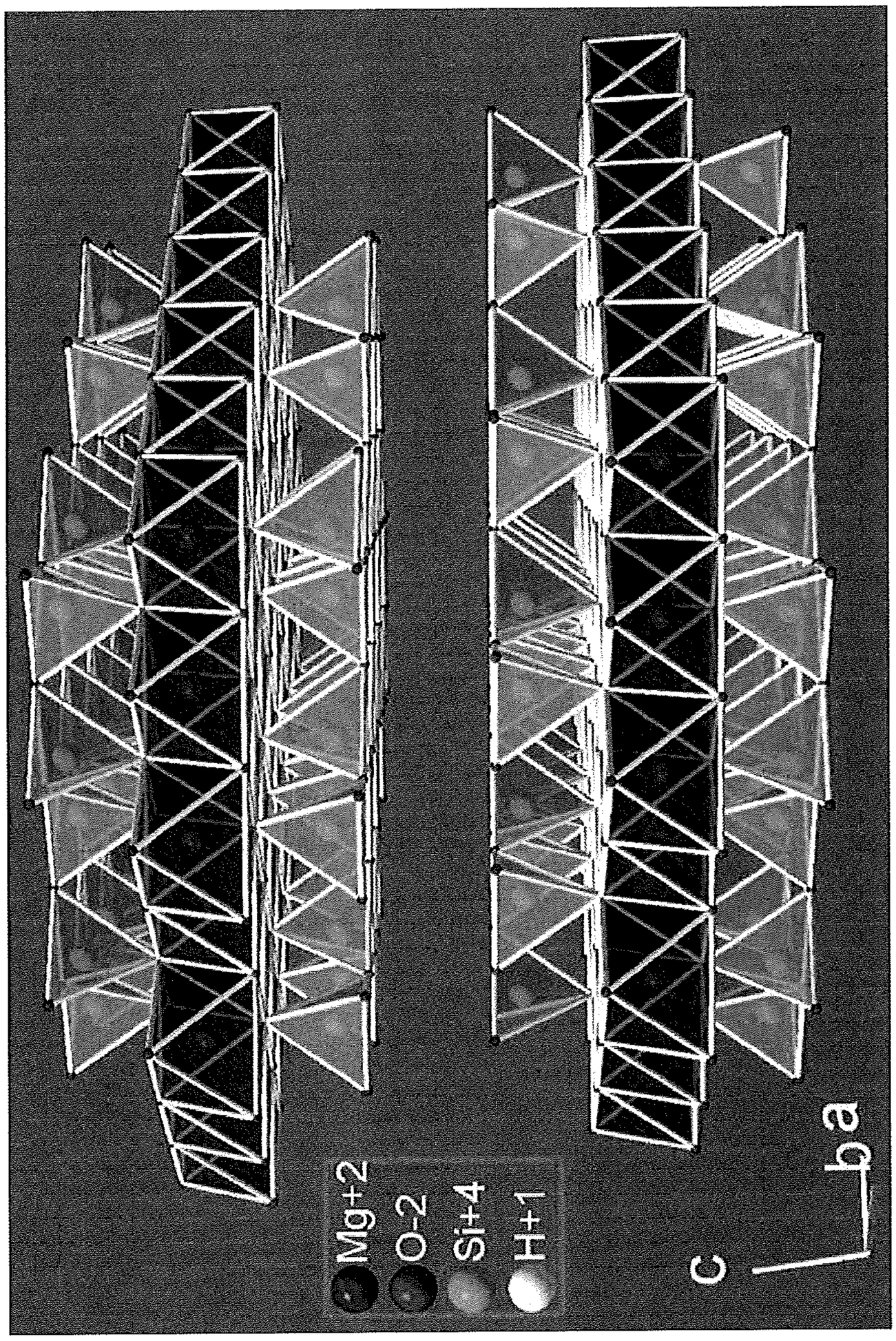

Figure 1.1 Schematic structure of talc

From NIMSoffice, http://en.wikipedia.org/wiki/File:Talc.GIF

formed when talc plates elongate parallel to the a axis within the plate to form true ribbon-like fibres of talc. These fibres may occur in an asbestiform habit consisting of bundles of narrow fibres randomly oriented around the axis of elongation (c axis). In some deposits, including those in the Gouverneur District of New York State, a small proportion of talc fibres are intergrown on a nanoscale with amphiboles (Stemple & Brindley, 1960; Greenwood, 1998; Wylie *et al.*, 1997).

Chemical composition: The ideal formula is $Mg_3Si_4O_{10}(OH)_2$. When expressed in the standard oxide form, the ideal chemical composition is: 31.9% MgO, 63.4% SiO_2 and 4.8% H_2O (Piniazkiewicz *et al.*, 1994). No talc is ideal, and small amounts of aluminium and iron are common impurities. Aluminium may substitute for both magnesium and silicon; iron(II) and iron(III) may substitute for magnesium. Talc that has almost all magnesium substituted by iron is called minnesotaite and is abundant in the iron formations of Minnesota, USA (Deer *et al.*, 1962). Fluorine is the most common substitution for the hydroxy group (Petit, 2005). Small amounts of nickel, chromium, calcium, potassium, sodium and manganese are also found in the octahedral sites while titanium may substitute for silicon in the tetrahedral site. Table 1.2 provides examples of the variability in the composition of mineral talcs, talc ores and talc products.

Solubility: The solubility of talc has been described in detail by Jurinski and Rimstidt (2001). On the sole basis of dissolution under pulmonary conditions, authors estimated that the maximum residence time in the lung of a 1-μm 'spherical' particle of talc is approximately 8 years. The reader is referred to Section 4 for a detailed description of the kinetics of deposition and clearance.

1.1.4 *Chemical and mineralogical characteristics of talc deposits*

Talc ore deposits are formed from the hydrothermal metasomatism of pre-existing rocks by fluids that contain silicon and/or magnesium. Hydrothermal fluids may be derived from fluids that migrate during retrograde or prograde regional metamorphism or from contact metamorphism that is associated with nearby or distant intrusive igneous rocks. The chemical composition of talc and its associated minerals result from the original rock type, the nature of the hydrothermal alteration and metamorphic history (Harben & Kuzvart, 1996).

The chemical and mineral compositions of talc from various locations are shown in Tables 1.2 and 1.3, respectively.

(a) Talc derived from mafic and ultramafic rocks

Talc deposits, the protoliths of which are ultramafic (or mafic) rocks, are abundant in number but small in total production. They are found in discontinuous bodies in orogenic belts, such as the Alps, the Appalachians and the Himalayas, and form during the regional metamorphism that accompanies orogenesis. They also occur in Canada (Ontario and Quebec), Egypt, Finland, Germany, Norway, the Russian Federation (Shabry and Miassy),

Table 1.2 Chemical composition (wt%) of selected mineral talcs, talc ores and talc mineral products

Component	Mineral talc[a,b]									Talc ores[c]									
	1	2	3	4	5	6	7	8	9	1[d]	2[d]	3[d]	4[d]	5[e]	6[e]	7[e]	8[e]	9[f]	10[g]
SiO_2	62.61	62.67	62.47	62.16	60.06	60.02	60.88	61.07	51.29	70.8	49.8	44.6	44.8	35.98	59.15	62.65	59.80	54.92	60
TiO_2	–	–	–	–	–	–	0.10	–	0.04	0.07	0.03	0.03	0.06	0.02	–	–	–		
Al_2O_3	–	0.38	0.47	0.88	1.60	1.88	1.98	2.42	0.61	0.69	0.48	0.45	1.20	0.43	0.26	0.31	0.57		0.70
Fe_2O_3	–	0.68	–	–	–	–	0.83	1.49	2.00	0.86	0.29	0.51	0.46	0.65	3.36	1.51	0.05	0.46	2.2
FeO	2.46	0.65	0.79	1.41	1.74	1.51	–	–	33.66	–	–	–	–	5.96	–	–	0.15		
MnO	0.01	–	0.00	–	–	–	–	–	0.12	0.01	0.02	0.03	0.03	0.41	–	–	0.39		
MgO	30.22	29.95	31.76	30.86	30.83	30.39	31.18	29.13	6.26	23.2	19.9	23.2	25.0	32.95	31.34	30.23	27.45	27.20	31
CaO	–	1.35	0.00	–	0.40	1.00	0.14	0.75	0.00	0.07	10.4	14.7	9.98	0.00	0.15	Trace	6.80	5.76	
Na_2O	–	–	–	–	–	–	–	–	0.08	<0.15	<0.15	<0.15	0.59	0.00	–	0.15	–		
K_2O	–	–	–	–	–	–	–	–	0.03	<0.02	0.31	<0.02	0.93	0.00	–	0.05	–		
Loss on ignition										3.99	18.1	16.0	16.1	23.18	6.06	5.14	5.93	10.76	5.80
NiO										–	–	–	–	0.21	–	–	–		
Cr_2O_3														0.18					
H_2O^+	4.72	5.05	4.70	4.92	5.02	5.37	4.98	4.82	5.54										
H_2O^-	–	–	0.06	–	–	0.32	–	–	0.24										

[a] From Deer *et al.* (1962)
[b] 1, Talc, altered periodotite (Muruhatten, northern Sweden); 2, Talc (Shabrov, Urals, USSR); 3, Talc (Murphy, NC, USA); 4, Light-green talc (Malangen, Norway); 5, Green talc, altered serpentine (Parma district, Apennines, Italy); 6, Black talc, with carbonaceous material derived from a bluish gray rock (Parma, Apennines, Italy); 7, Talc (Mount Fitton, South Australia); 8, Talc, altered tremolite (Yellandu Warangal district, Hyderabad, India); 9, Greenish gray iron talc (minnesotaite) (East Mesabi range, MN, USA)
[c] 1, Talc rock (Alliance Mine, CA, USA); 2, Talc ore (Pleasanton Mine, CA, USA); 3, Talc ore (Talc City, USA); 4, Talc ore (Acme Mine, CA, USA); 5, Vermont talc–magnesite ore (USA); 6, Flotation product (Johnson, VT, USA); 7, Steatite (Yellowstone Mine, MT, <USA); 8, Average ore (Talcville, NY, USA); 9, Texas talc (USA); 10, FINNTALC M30
[d] From Van Gosen *et al.* (2004)
[e] From Chidester *et al.* (1964)
[f] From Pence (1955)
[g] From Mondo Minerals (2005)

southern Spain and the USA (Arkansas, California and Texas) (Piniazkiewicz *et al.*, 1994; Harben & Kuzvart, 1996). These deposits may contain trace amounts of nickel, cobalt and chromium that are derived from their ultramafic protolith. One major talc deposit in eastern USA contains substantial amounts of nickel (up to 0.2%; Rohl *et al.*, 1976). Nickel-substituted talc is also associated with serpentine bodies, at up to 0.5% by weight (Pooley & Rowlands, 1975); pentlandite has been reported in talc from Finland from which it is recovered by flotation (Harben & Kuzvart, 1996). Quartz is uncommon in talc that has mafic or ultramafic protoliths and the fluorine content is generally low (Ross *et al.*, 1968). Chlorite and amphiboles are usually associated with this type of talc deposit although they are commonly separated in space from the talc ore (Vermont). The amphiboles may or may not be asbestiform, depending on the local geological history. A small amount of amphibole asbestos is associated with this type of talc deposit at Soapstone Ridge, GA (USA) and anthophyllite asbestos is abundant in the vicinity of the talc at Dadeville, AL (USA) (Van Gosen *et al.*, 2004). In a few deposits, the parent was mafic rock (Virginia (Schuyler), Georgia and Egypt) (Harben & Kuzvart, 1996).

Table 1.3. Mineral composition (wt%) of talc from various locations

Mineral	Montana	Vermont	North Carolina	New York[a]	California	France
Talc	90–95	80–92	80–92	35–60	85–90	70–90
Tremolite	–	–	–	30–55	0–12	–
Anthophylite	–	–	0–5	3–10	–	–
Serpentine	–	–	–	2–5	–	–
Quartz	<1	<1	1–3	1–3	<1	<1
Chlorite	2–4	2–4	5–7	–	–	10–30
Dolomite	1–3	1–3	2–4	0–2	0–3	–
Calcite	–	–	–	1–2	–	–
Magnesite	0–5	0–5	–	1–3	–	–

From Harben & Kuzvart (1996)
[a] Gouverneur District

(b) Talc derived from magnesium carbonates

Talc deposits formed from the alteration of carbonate and sandy carbonate such as dolomite and limestone are the most important in terms of world production. Two types are recognized: (i) those derived from hydrothermal alteration of unmetamorphosed or minimally metamorphosed dolomite (Australia (Mount Seabrook and Three Springs), China, India, Republic of Korea, the Russian Federation (Onot), northern Spain (Respina) and the USA (Alabama (Winterboro), California (Talc City), Montana (Yellowstone), Washington (Metaline Falls) and West Texas); and (ii) those derived from hydrothermal alteration (including retrograde metamorphism) of regionally metamorphosed siliceous dolomites and other magnesium-rich rocks (Austria (Leogen), Brazil (Brumado), Canada

(Madoc), France (Trimouns), Germany (Wunsiedel), Italy (Chisone Valley), the Russian Federation (Krasnoyarsk), Slovakia (Gemerska Poloma), Spain and the USA (Chatsworth, GA, Death Valley–Kingston Range, CA, Murphy Marble belt, NC, and New York). In a few of these deposits, including the large deposit at Trimouns, France, the talc may be classified as being derived from alumino-silicate rocks (Harben & Kuzvart, 1996; Luzenac, 2004).

Talc derived from magnesium carbonate may contain quartz. Van Gosen *et al.* (2004) suggested that, among the first group, only those that are formed by hydrothermal alteration of dolomites that are in direct contact with igneous bodies are probably accompanied by amphiboles (e.g. Death Valley, CA, USA) and that hydrothermal deposits in carbonates that are formed by relatively low-temperature fluids derived from distant igneous bodies contain no or only very minor amounts of amphibole (Talc City, CA, Southwestern Montana and Allamoore, TX, USA). In some deposits in the second group, amphiboles may be very abundant, especially those formed during high-temperature regional metamorphism of impure dolomites. In the Gouverneur District New York State, for example, non-asbestiform tremolite comprises between 30 and 70% of the talc product (Harben & Kuzvart, 1996).

Gouverneur District New York State talc that is currently marketed under the trade name Nytal is a unique industrial mineral product that can readily be distinguished from all other commercially available industrial talcs based on its mineral content. Nytal 100, for example, contains 30–50% tremolite, 20–40% talc, 20–30% serpentine, 2–10% anthophyllite and 0.14% quartz (R.T. Vanderbilt Company, 2000). The tremolite, anthophyllite and serpentine occur as mineral fragments and not as asbestiform fibres. Tremolite from this deposit has been characterized in detail (Campbell *et al.*, 1980). Nytal also contains asbestiform fibres of talc and talc intergrown on a nanoscale with amphibole (Wylie *et al.*, 1997). Wylie *et al.* (1997) estimated that the abundance of particles that are longer than 5 μm and have an aspect ratio of 3:1 or greater in sample FD14 (identified as a commercial talc product from New York State) is 0.8×10^3/μg; 62% of these particles were identified as talc, 24% as fragments of tremolite plus a small amount of anthophyllite and 14% as talc intergrown with anthophyllite. Products from other mines in this district before 1964 contained different proportions of anthophyllite and tremolite, which may be asbestiform (Chidester *et al.*, 1964).

(c) Minerals associated with talc

Because talc deposits are formed from different protoliths under many different geological conditions, each talc deposit has a combination of mineralogy and mineral habit that is distinctive and, in many cases, unique. The most common minerals found in talc products include chlorite, magnesite, dolomite, tremolite, anthophyllite, serpentine and quartz. However, many other minerals have been reported; these are given in Table 1.4 (Pooley & Rowlands, 1975; Piniazkiewicz *et al.*, 1994; Harben & Kuzvart, 1996). Some of these minerals are beneficial to certain applications such as tremolite in ceramics.

Table 1.4. Minerals commonly associated with talc

Mineral group	Name	Ideal formula
Carbonate	Dolomite	$(Ca,Mg)CO_3$
	Magnesite	$MgCO_3$
	Breunnerite	$(Mg,Fe)CO_3$
	Calcite	$CaCO_3$
	Siderite	$FeCO_3$
	Ankerite	$Ca(Fe,Mg,Mn)(CO_3)_2$
Phyllosilicates	Chlorite	$(Mg,Al,Fe)_{12}(Si,Al)_8O_{20}(OH)_{16}$
	Serpentine (lizardite and antigorite)	$Mg_3Si_2O_5(OH)_4$
	Phlogopite (mica)	$K_2(Mg,Fe)_6Si_6Al_2O_{20}(OH)_4$
	Sepiolite	$Mg_8Si_{12}O_{30}(OH)_4(H_2O)_4$
Amphibole[a]	Tremolite	$Ca_2Mg_5Si_8O_{22}(OH)_2$
	Anthophyllite	$(Mg,Fe)_7\ Si_8O_{22}(OH)_2$
	Actinolite	$Ca_2(Mg,Fe)_5\ Si_8O_{22}(OH)_2$
Tectosilicates	Quartz	SiO_2
	Feldspar	$(K,Na)AlSi_3O_8$
Oxides	Magnetite	Fe_3O_4
	Ilmenite	$FeTi\ O_3$
	Manganese oxide	MnO_2
	Rutile	$Ti\ O_2$
Sufides	Pyrite	FeS_2
	Pyrrhotite	FeS
	Pentlandite	$(Fe,Ni)_9S_8$
Other minerals	Tourmaline[b]	$NaFe_3Al_6(BO_3)_3Si_6O_{18}(OH)_3(OH)$
	Graphite	C

Compiled by the Working Group from Pooley & Rowlands (1975); Piniazkiewicz *et al.* (1994); Harben & Kuzvart (1996)
[a] See Leake *et al.* (1997) for precise nomenclature and chemical composition of the amphibole group.
[b] This is the formula for one member of the tourmaline group; chemistry is highly variable.

(d) Chemical composition of talc ore

The variability in the chemical composition of talc ore, talc mineral products and talc rock primarily reflects their mineral composition (see Table 1.2).

1.1.5 *Processing of talc ores and composition of talc products*

Talc ores may be processed by a variety of techniques that include selective mining, hand sorting and milling by roller mills, hammer mills, ball mills, fluid energy mills and jet mills and are classified and separated from other minerals by froth flotation or magnetic separation. Some may be treated with acid and calcined. The particle sizes of talc and the abundance of the associated minerals are determined by characteristics of the ore, methods of processing, and the duration of grinding. Grinding breaks the talc platelets along (001) and disaggregates the particles; prolonged grinding may destroy the crystallinity (Sanchez-Soto *et al.*, 1997; Zbik & Smart, 2005). Roller mills tend to preserve the platy structure and different types of milling affect properties such as flatness, surface roughness, roundness, width and elongation (Yekeler *et al.*, 2004). Talc particles are platy, and sizes reflect the dimension parallel to the plate; data are not available on the thinness of the plates.

Talc products also vary in particle size; median sizes range from ~1 to >20 μm and top sizes range from <10 to >100 μm. The most common designations for fineness are based on US Sieve Series and Tyler equivalence and include 200 mesh (95–98% <74 μm), 325 mesh (95–99% <44 μm) and 400 mesh (95–99% <37 μm) (Zazenski *et al.*, 1995).

Talc products that contain >95% mineral talc are used in cosmetics, baby powder, pharmaceuticals, steatite ceramics, pitch control in the paper industry and as a filler in rubber. Today, the talc in baby powders is >99% 200 mesh (Zazenski *et al.*, 1995). Talc products that contain between 75 and 95% mineral talc are used in paper fillers, reinforced plastics, paint, ceramics and dusting compounds for rubber. Lower-purity talc is used in roofing material, patching compounds, flooring and fertilizers (Piniazkiewicz *et al.*, 1994). Particle sizes, colour and nature of associated minerals also vary among these applications.

1.1.6 *Analysis*

(a) Analysis of bulk samples

Talc can be identified from its optical properties by polarized light microscopy and oil immersion, from its X-ray or electron diffraction pattern, from its chemical composition and from differential thermal analysis/thermal gravimetric analysis. Chlorite has similar optical properties. Talc platelets on end and talc intergrown with amphibole in fibrous talc have complex electron diffraction patterns that may resemble other silicates, including amphiboles (Stemple & Brindley, 1960) and sepiolite (Germine, 1987), unless carefully indexed. Anthophyllite and sepiolite have chemical compositions that are very similar to talc and require quantitative chemical analysis to differentiate them, including the use of well characterized standards in the case of dispersive X-ray analysis used in conjunction with electron microscopy. Identification of mixed mineral assemblages by X-ray

diffraction may be difficult because of pattern overlap (Krause, 1977) and X-ray diffraction cannot distinguish asbestiform minerals from other habits.

Particle size distributions that are determined by settling underestimate the abundance of larger particles and overestimate the number of smaller particles because the platy structure results in longer settling times for talc compared with spherically shaped particles of equivalent size. Computer-controlled scanning electron microscopy has been used to provide a more accurate size distribution. Determination of the respirable fraction of bulk materials by these two methods differs significantly (Zazenski *et al.*, 1995).

(b) Analysis of exposure

The standard methods for the analysis of airborne exposures in an occupational setting where asbestos is known to be present include those of the Health and Safety Executive (1995) and the Occupational Safety and Health Administration (2005). These methods were designed to provide an index of exposure since they count only particles longer than 5 μm with a length-to-width ratio of 3:1 or more that are visible by phase-contrast microscopy. They do not determine the mineral identity of the particles counted. In a mining environment where many minerals form elongated fragments, the results of fibre counts can be difficult to interpret. In bulk samples of talcum products, for example, Cralley *et al.* (1968) reported that particles longer than 5 μm with a 3:1 aspect ratio in 22 talcum products represented 19% of the particles, which were predominantly talc.

Conversion of fibre counts to gravimetrically based exposure metrics is complicated as this will depend on the particle size. Oestenstad *et al.* (2002) adjusted million particles per cubic foot (mppcf) to milligrams per cubic metre (mg/m^3) using the following regression equation:

$$\ln (mg/m3)=\ln (mppcf)\times 0.62–1.20$$

All gravimetric measurements to monitor exposure to talc in occupational settings are taken from samples of respirable dust particles. The reader is referred to the Glossary and the monograph on carbon black for further details.

1.2 Production and use

1.2.1 *Production*

Talc deposits result from the transformation of existing rocks under hydrothermal activity and are classified according to the parent rock from which they derive. There are three broad types of talc deposit of commercial significance (Luzenac, 2004; EUROTALC, 2005; Industrial Minerals Association-Europe, 2005): (i) talc derived from mafic and ultramafic rocks, which provides about 40% of talc supplies; the crude ore is usually grey and, to be commercially viable, may be upgraded to improve the mineralogy and whiteness (generally by flotation); (ii) talc derived from magnesium carbonates, which provides >50% of world production; and (iii) talc derived from alumino-silicate

rocks, from which about 10% of world production is mined, and which is sometimes found in combination with deposits of magnesium carbonate; the crude ore is generally grey due to the presence of chlorite, but no upgrading is necessary as chlorite performs adequately in the applications of interest.

This wide diversity of origins and types of deposit naturally gives rise to a wide variety of ores and product grades that differ according to their mineralogical composition, colour and crystalline structure (microcrystalline or lamellar) (Luzenac, 2004; EUROTALC, 2005; Industrial Minerals Association-Europe, 2005).

World production of talc and pyrophyllite in both 2003 and 2004 was estimated to be 8.3 million tonnes. Of the total production, approximately 2.15 million tonnes were confirmed to be used for talc production in both 2003 and 2004. China was the leading producer of talc in the world, followed by the USA, India, Brazil (crude) and France (crude). The Republic of Korea was the leading producer of pyrophyllite, followed by Japan and Brazil. Brazil, China, France, India, Japan, the Republic of Korea and the USA produced 84% of talc and pyrophyllite in the world (Table 1.5) (Virta, 2004).

Table 1.5. World production of talc (in tonnes unless otherwise specified)[a,b]

Country	2000	2001	2002	2003	2004
Argentina	6730	1665	1643	1759	1800
Australia[c]	178 545	173 446	173 741	174 000	173 000
Austria (crude+so)[d]	130 000[e]	140 000	135 000	135 000	135 000
Bhutan[d]	3700	3800	3900	3900	3900
Brazil (crude)	300 000	397 000	348 000	365 000	370 000
Brazil (marketable product)[f]	7049	6300	5617	5593	5600
Canada (t+p+so)	86 000	90 000	90 000	90 000	90 000
Chile	2421	4177	3537	4374	4400
China (unspecified)[d]	3 500 000	3 500 000	2 500 000	3 000 000	3 000 000
Colombia (t+p+so)[d]	15 000	15 000	15 000	15 000	15 000
Egypt (t+p+so+st)[d]	40 000	40 000	40 000	40 000	40 000
France (crude)[d]	350 000	350 000	350 000	350 000	350 000
Germany (marketable+st+t)[d]	8000	10 000	10 000	10 000	10 000
Hungary[d]	500	500	500	500	500
India (st)	545 000	546 000	550 000	552 000	550 000
Iran[d,g]	25 000	25 000	25 000	25 000	30 000
Italy (t+st)[d]	140 000	140 000	140 000	140 000	140 000
Japan	50 000	45 000	40 000	40 000	35 000
Macedonia	562	557	550	550	600
Mexico	20 569	77 650	111 621	114 870	115 000
Morocco	12 522	27 246	39 612	1959	2000
Nepal[h]	5852	3923	2621	2500	2400
Norway (t+so+st)[d]	27 000	27 000	28 000	28 000	28 000
North Korea (unspecified)[d]	120 000	120 000	110 000	110 000	110 000
Paraguay (t+p+so)[d]	200	200	200	200	200
Peru	9668	11 165	10 685	10 791	10 000
Portugal[d]	8200	8200	8200	8200	8000
Republic of Korea	11 344	47 712	37 863	47 911	48 000
Romania	7850	7270	7292	10 082	10 000
Russia[d]	100 000	100 000	100 000	100 000	100 000

Table 1.5 (contd)

Country	2000	2001	2002	2003	2004
Slovakia	1800	2600	2290	1000	1500
South Africa	5600	3218	2511	4472	12 065[e]
Spain (t+st)[d]	100 000	100 000	100 000	100 000	100 000
Sweden (t+so)	20 000	15 000	15 000	15 000	14 000
Taiwan	–	130	27	466	411[e]
Thailand	7390	6838	1702	8501	8500
United Kingdom (t+p+so)[d]	5000	5000	5000	5000	5000
USA	851 000	863 000	828 000	840 000	857 000[e]
Uruguay (t+p+so)	2903	1694	1700	1700	1700
Zimbabwe	989	1273	911	196	–[e]

From Virta (2004)
p, pyrophyllite; so, soapstone; st, steatite; t, talc
[a] World totals; data from the USA and estimated data are rounded to no more than three significant digits; may not add to totals shown.
[b] Table includes data available through to April 19 2005.
[c] Data based on Australian fiscal year ending 30 June of the year stated.
[d] estimated
[e] Reported figure
[f] Direct sales and/or beneficiated (marketable product)
[g] Data based on Iranian fiscal year beginning 21 March of the year stated
[h] Data based on Nepalese fiscal year beginning mid-July of the year stated

1.2.2 *Use*

The properties of mineral talc (platyness, softness, hydrophobicity, organophilicity and inertness) and the mineralogical composition of talc products govern their specific applications in many industries and processes including paint, polymers, paper, ceramics, animal feed, rubber, roofing, fertilizers, cosmetics and pharmaceuticals. The principal technical applications of talc in commercial products are as an anti-sticking and anti-caking agent, lubricant, carrier, thickener, strengthening and smoothing filler and absorbent (Industrial Minerals Association-Europe, 2005).

(a) End-use categories

(i) *Agriculture and food*

Talc is used as an anti-caking agent, dispersing agent and die lubricant in animal feed and fertilizers. In premixes and agricultural chemicals, it is used as an inert carrier. Talc is also used as an anti-stick coating agent in several foods and as a processing aid in the production of olive oil. (Luzenac, 2004; Industrial Minerals Association-Europe, 2005).

Agricultural chemicals. Talc is a functional carrier in agricultural products that offers very low moisture equilibrium, relative hydrophobicity and chemical inertness. Costs are reduced by extending expensive chemicals and improving the dispersion and flow of

active ingredients. Talc is appropriate for garden dusts, flea and tick powders, seed treatments and biocides (Luzenac, 2004).

Anti-caking and homogenization. Talc improves the flowability of difficult raw materials, e.g. oilseed meal and finished products, and feeds with high loads of sticky ingredients such as molasses, oil, fatty products, urea, milk powder and sugar. The smooth and flat lamellae of talc cover each particle and help them to flow freely. As they are naturally water-repellent, talc particles form a barrier when they envelop other particles and reduce the evaporation and uptake of water within the product mass. Talc platelets help different constituents to blend more easily and facilitate the dispersion of sticky ingredients (Luzenac, 2004).

Die lubricant. Talc is a cost-effective die lubricant especially for high-fibre, high-sugar and high-mineral formulations and pelleted feeds (Luzenac, 2004).

Fertilizers. Talc is used as an anti-caking agent in both prilled (pelleted or granulated) ammonium nitrate and granular fertilizers. Talc particles reduce the absorption of moisture and prevent the formation of hydrate bridges, which enables longer storage periods. In Europe, amine-coated talcs are marketed with enhanced adhesion properties that enable the amine contents to be reduced and result in lower dust levels and less environmental impact (Luzenac, 2004).

Foods. Talc is an effective anti-stick coating agent that is used in several foods, such as chewing gum, candies and cured meats (Luzenac, 2004).

Processing of olive oil. In the production of olive oil, talc acts as a natural processing aid that improves extraction and increases the yield of virgin olive oil (Luzenac, 2004).

Premixes. Talc is used as an inert carrier for active premix ingredients. Certain talc grades have been specifically designed for dust-free, high-specification requirements (Luzenac, 2004).

(ii) *Ceramics*

Talc imparts a wide range of properties to floor and wall tiles and sanitary ware, tableware, refractory goods and technical ceramic products. In traditional building ceramics (tiles and sanitary ware), it is used essentially as a flux to enable firing temperatures and cycles to be reduced. In refractory applications, talcs that are rich in chlorite are used to improve thermal shock resistance. Talcs with a microcrystalline form are the most appropriate for steatite ceramics. During firing, the talc is transformed into enstatite, which possesses electro-insulating properties. Talcs with a very low iron content are particularly suitable for use in frit, engobe [underglaze] and glaze compositions (Luzenac, 2004; Industrial Minerals Association-Europe, 2005).

(iii) *Coatings*

Talcs confer several properties on coatings. In interior and exterior decorative paints, they act as extenders to improve hiding power and the efficiency of titanium dioxide. The lamellar platelets of talc make paint easier to apply and improve cracking resistance and sagging, and also enhance matting. In anti-corrosion primers, talcs are used to improve

resistance to corrosion and adhesion of the paint. They are also used in inks, jointing compounds, putties and adhesives (Luzenac, 2004; Industrial Minerals Association-Europe, 2005).

(iv) *Paper*

Talcs are used in both uncoated and coated rotogravure papers in which they improve printability, reduce surface friction and enhance handling characteristics. They also improve mattness and reduce ink scuff on offset papers. When used as pitch-control agents, talcs 'clean' the papermaking process by adsorbing any sticky resinous particles in the pulp onto their platy surfaces, and thereby prevent the agglomeration and deposition of these on the felts and calenders. In contrast to chemical pitch-control products that pollute the process water, talc is removed with the pulp, which enables the papermaker to operate more easily in a closed circuit. In specialty papers such as coloured papers or labels, talcs help to improve quality and productivity (Luzenac, 2004; Industrial Minerals Association-Europe, 2005).

(v) *Personal care*

As it is soft to the touch and inert, talc has been valued for centuries as a body powder. Today, it also plays an important role in many cosmetic products, including products for feminine hygiene and baby powders, and provides the silkiness in blushes, powder compacts and eye shadows, the transparency of foundations and the sheen of beauty creams. In pharmaceutical products, talc is an important excipient that is used as a glidant, lubricant and diluent. Soap manufacturers also use talc to enhance the performance of skin care products (Luzenac, 2004; Industrial Minerals Association-Europe, 2005). Table 1.6 presents information on levels of talc in cosmetic products in the USA and Table 1.7 gives the composition of some examples of products that are used for body care.

(vi) *Plastics*

Talcs impart a variety of properties to polypropylene, such as greater stiffness and improved dimensional stability in automotive parts, household appliances and white goods. Advanced milling technology is required to obtain the finest talcs without diminishing the reinforcing power of their lamellar structure. Talcs are also used for the anti-blocking of linear low-density polyethylene and as a nucleating agent in semicrystalline polymers. In polypropylene that is used in food packaging applications, talc is a highly effective reinforcing filler. The grades of talc used for this purpose include calcined, surface-treated, ultrafine grind and high aspect ratio (Luzenac, 2004; Industrial Minerals Association-Europe, 2005).

(vii) *Roofing*

Talc is a high-performance product that is used to back surfacing asphalt shingles. The use of talc is even more important in the growing market for laminated shingles in

which handling is more complex, wear and tear on machinery is greater, cutting is doubled and adhesion of the interlayer is critical (Luzenac, 2004).

Table 1.6. The number of cosmetic products in the Cosmetics and Toiletries Formulations Database in the USA that contain talc or talcum

Product categories	No. of products
Antiperspirants and deodorants	22
Baby products	6
Bath and shower products	2
Beauty aids[a]	184
Creams	14
Hair care products	1
Lipsticks	5
Lotions	1
Shampoos	1
Shaving products	2
Sun care products	3
Miscellaneous[b]	8

Compiled by the Working Group from Flick (2005)
[a] Beauty aids includes aerosol talc products, face masks, foundations, body oils, make-up bases, concealers, blushes, body powders, rouge, make-up, compact powders, eye shadows, dusting powders, eyebrow pencils, pressed powder products, face powders, mascaras, liquid talc products and powder cleansers
[b] Miscellaneous includes aerosol talc foams, wound ointments, foundations with extracts, foot powders, liquid foundations and sport tints

(viii) Rubber

Talcs reduce the viscosity of rubber compounds and thereby facilitate the processing of moulded parts. They also improve the quality of extrudates, which increases production rates and enhances the resistance to ultraviolet (UV) radiation of exterior parts such as automotive profiles. In sealants and gaskets, they provide compression resistance, while in pharmaceutical stoppers, they create a barrier against liquids. Talcs are used as insulators in cables and as processing aids in tyre manufacture (Luzenac, 2004; Industrial Minerals Association-Europe, 2005).

Table 1.7. Composition of some products used for body care

Product	Wt% talc	Other components	Wt% other components
Dusting powder	97.7	Perfume oil	0.8
		GLUCAM P-20	1.5
		Preservative	q.s.
Dusting powder	91.6	Magnesium carbonate	3.0
		Zinc stearate	3.0
		Triclosan	0.2
		Perfume oil	0.7
		GLUCAM P-20	1.5
		Preservative	q.s.
Velvety dusting powder	77.4	Aluminum starch, Octenyl succinate	20.0
		Zinc stearate	2.0
		Methylparaben	0.10
		Propylparaben	0.10
		Germall II	0.20
		Fragrance	0.20
Face and body powder	89.30	Boron nitride	10.00
		Methylparaben	0.15
		Propylparaben	0.20
		Imidazolidinyl urea	0.05
		Iron oxide (yellow)	0.20
		Iron oxide (red)	0.10
Baby powder	72	DYNASAN 114	2.0
		Magnesium stearate	8.0
		Kaolin	18.0
After-bath talc	92.5	Perfume oil	5.0
		PPG-20 methyl glucose ether	1.50
		Macadamia nut oil	1.00
Body powder	4.0	Boron nitride	5.0
		Silica	2.5
		Starch	30.2
		Kaolin	10.0
		Magnesium stearate	1.00
		Bentone 38/Quaternium18, Hectorite	1.0
		Isopropyl myristate	6.0
		Perfume	1.8
		Pigments	q.s

Table 1.7 (contd)

Product	Wt% talc	Other components	Wt% other components
Powder for babies and children	20.0	Kaolin	20.0
		Rice starch	51.0
		Zinc stearate	5.0
		Eutanol G	2.0
		Lanette O	2.0
Dispersing bath powder	0	Kukui nut oil	1.0
		Phenyl trimethicone	1.0
		Cyclomethicone	2.0
		Fragrance	1.5
		Ethoxydiglycol	2.0
		Oleth-2	2.50
		Oleamidopropyl PG, dimonium chlorite	2.0
		Topopheryl acetate (Vitamin E)	0.50
		Cornstarch	86.00
		Silica	1.50
Body powder	0	Zinc stearate	5.0
		Zinc oxide	5.0
		Magnesium carbonate	15.0
		Kaopolite TLC	75.0
Talc-free body powder	0	Cornstarch	88.45
		Kaolin	5.0
		Mica	2.0
		Titanium dioxide	2.0
		Red mica and titanium dioxide	0.25
		Tapioca starch	2.0
		Methylparaben	0.10
		Propylparaben	0.05
		Imidazolinidyl urea	0.15

From Flick (2005)
The Working Group was aware that these data are not representative of all products
q.s., quantum satis (sufficient quantity)

(ix) *Wastewater treatment*

Specialty talc can improve the performance of biological wastewater treatment plants. The talc particles ballast the flocs of bacteria and accelerate their sedimentation (Industrial Minerals Association-Europe, 2005).

(x) *Other*

Talc is used as an anti-sticking agent to powder moulds in foundries and in the manufacture of pharmaceuticals and rubber or on conveyor belts that carry foodstuffs. It is also used in other products, such as condoms and surgery gloves. Particle-wood boards (chip boards) are powdered with talc to avoid sticking when stockpiled. Talcs are also used as smooth fillers, for example in the 'lead' of colouring pencils and in putties (where it can be the major component) (Industrial Minerals Association-Europe, 2005).

Talc had been used as a sclerosing agent in the pleural space for the treatment of spontaneous pneumothoraces. Talc is also used for pleurodesis in the treatment of malignant pleural effusions (Dresler *et al.*, 2005). The products used for these purposes contain 95% talc and 5% chlorite and dolomite.

(b) Use patterns

The worldwide use pattern for talc in 2000 was: paper, 30%; ceramics, 28%; refractories, 11%; plastics, 6%; a filler or pigment in paints, 5%; roofing, 5%; cement, 3%; cosmetics, 2%; and other miscellaneous uses, 10% (art sculpture, asphalt filler, autobody filler, construction caulks, agriculture and food, flooring and joint compounds) (Roskill Information Services Ltd, 2003). The use pattern for talc in the USA in 2004 was: ceramics, 32%; paints, 19%; paper, 16%; roofing, 6%; plastics, 4%; rubber, 3%; cosmetics, 1%; and other, 19% (Virta, 2004). The use of talc in cosmetics in the USA decreased from 34 000 tonnes in 1993 to 5000 tonnes in 2004 (Virta, 2004).

The estimated world consumption of talc by geographical region in 2000 was: Asia, 43%; western Europe, 19%; North and central America, 17%; South America, 8%; Indian subcontinent and Middle East, 8%; Africa, 2%; eastern Europe and Commonwealth of Independent States countries, 2%; and Australia and New Zealand, 1% (Roskill Information Services Ltd, 2003).

1.3 Occurrence and exposure

1.3.1 *Natural occurrence*

Talc is found in small amounts in metamorphic mafic and ultramafic rocks and in carbonates. These metamorphic rocks crop out in mountain belts such as the Alps, the Appalachians and the Himalayas and in ancient continental shields such as the Canadian shield in New York and Canada.

The occurrence of talc deposits of commercial importance is described extensively in Section 1.1.4.

1.3.2 *Occupational exposure*

Exposure to talc dust occurs during its mining, crushing, separating, bagging and loading and in various industries that use talc (see Section 1.2.2). This section reviews

exposure to talc during its mining and milling, other than that from the Gouverneur District New York State mines, and in user industries, whenever this information is available. Exposure to talc is also described, where possible, for those industries in which epidemiological studies have been carried out in relation to the occurrence of cancer.

(a) Mining and milling

Before the 1970s, exposure measurements were made by collecting particles in an impinger and counting them by optical microscopy. Concentrations were thus expressed as million particles per cubic foot of air (mppcf). More recent studies have described levels of exposure to dust that were assessed using gravimetric measurement techniques.

Table 1.8 describes studies of exposure to talc in mines and mills. In Georgia, USA, average exposures to dust were 1440 mppcf (~50 854 particles/cm^3) for miners who used jackhammer drills and 52 mppcf (~1836 particles/cm^3) for millers. The talc was reported to contain 45% tremolite and 45% talc, with little or no quartz (Dreessen, 1933). Average dust concentrations in a talc mine were reported to range from 32 to 855 mppcf (~1130 to 30 195 particles/cm^3; six samples), whereas those in mills ranged from 17 to 1672 mppcf (~600 to 59 000 particles/cm^3; 14 samples). The dust was reported to contain 70% talc, 20–30% dolomite and 10% tremolite, and no quartz except for occasional fragments; its morphology was described as 'bladed crystals'. Highest exposures to dust occurred during bagging operations (Dreessen & DallaValle, 1935).

Concentrations of respirable dust in mass samples from three Vermont talc mines and mills surveyed in 1975–76 are given in Table 1.9. Geometric mean exposures to respirable dust ranged from 0.5 to 5.1 mg/m^3 in the mines and from 0.5 to 2.9 mg/m^3 in the mills; however, exposures in the mills were generally higher than those in the mines. Optical fibre counts as high as 60 fibres/cm^3 were reported. Subsequent analyses of these samples by scanning electron microscopy showed that they consisted of rolled talc and elongated talc particles. X-Ray diffraction analyses of bulk samples from these mines and mills showed that talc and magnesite were the major (20–100%) mineral components, chlorite and dolomite were minor (5–20%) components and calcite, quartz, biotite, ankerite, chromite, phlogopite and oligoclase were present in small amounts (<5%). Trace amounts of quartz were found in 15% of the samples (Boundy *et al.*, 1979). Dust from one closed mine was reported to contain tremolite microinclusions, but its fibrosity was not documented (Selevan *et al.*, 1979).

A cross-sectional study of occupational exposures in talc mines and mills in the USA was conducted by the National Institute for Occupational Safety and Health; the results are summarized in Table 1.10. Bulk samples from each region were analysed by transmission electron microscopy: no fibre was found in any sample of Montana talc; fibrous tremolite and antigorite were reported in Texan talcs (0.5–3.0 μm in diameter, 4–30 μm in length); and talcs from North Carolina contained particles with length:diameter ratios as high as 100:1, with some <0.1 μm in diameter (Greife, 1980; Gamble *et al.*, 1982). Van Gosen *et al.* (2004) recently reported that the Texan talc contained little or no amphibole.

Table 1.8. Studies of occupational exposures in talc mines and mills

Reference	Location of talc deposit	Date of exposure measurements	Method of measurement	Other minerals present
Dreessen (1933)	Georgia, USA	Pre-1933	Impinger	Tremolite
Dreessen & DallaValle (1935)	Georgia, USA	Pre-1935	Impinger	Tremolite, dolomite
Rubino *et al.* (1976); Coggiola *et al.* (2003)	Piedmont, Italy	1946–95	–	Quartz (radon, diesel exhaust)
Rubino *et al.* (1976)	Piedmont, Italy	1920–75	Impinger	Small amounts of tremolite
Boundy *et al.* (1979)	Vermont, USA	1975–76	Optical and electron microscopy fibre counts	Dolomite, calcite, magnesite, chlorite, traces of other minerals
Greife (1980); Gamble *et al.* (1982)	Montana, Texas and North Carolina, USA	1977–80	Gravimetric	Varied by location studied
Wild *et al.* (1995, 2002)	France, Austria	1986–92	Gravimetric (CIP personal sampler)	Quartz: France, <3%; Austria, <4%

CIP, capteur individuel de poussière [personal dust sampler]

Table 1.9. Concentrations (mg/m^3) of respirable dust in Vermont talc mines and mills

Company	Area	Summer 1975		Winter 1976	
		No. of samples	Geometric mean (mg/m^3)	No. of samples	Geometric mean (mg/m^3)
A	Underground mine	18	0.6	16	0.5
	Mill (1st shift)	4	1.7	13	1.7
	Mill (2nd shift)	6	0.5	3	1.5
B	Underground mine	15	1.5	23	0.9
	Mill (1st shift)	22	1.8	42	1.8
	Mill (2nd shift)	12	2.9	16	1.9
C	Underground mine	12	0.5	19	0.7
	Walk-in mine	7	1.2		
	Walk-in mine			6	1.7
	Open-pit mine	2	5.1	–	–
	Mill No. 1 (1st shift)	12	0.9	20	1.1
	Mill No. 1 (3rd shift)	3	0.8	4	1.4
	Mill No. 2 (1st shift)	11	1.0	8	0.5
	Mill No. 2 (2nd shift)	13	0.8	3	1.1

From Boundy *et al.* (1979)

Table 1.10. Concentrations of respirable dust in 275 samples from talc mines and mills located in Montana, Texas and North Carolina, USA

Samples	Geometric mean (mg/m^3)		
	Montana	Texas	North Carolina
From mines	0.66 (0.47–0.92)[a]	0.45 (0.18–0.71)	0.14 (0.07–0.31)
From mills	1.1 (0.85–1.41)	1.56 (0.96–2.54)	0.26 (1.13–0.51)
Bulk talc samples (% free silica)	<0.8	2.23	1.45

Adapted from Greife (1980); Gamble *et al.* (1982)
[a] In parentheses, 95% frequency interval

Analysis of 362 personal samples of respirable dust collected over a full shift from talc mines and mills by the Mine Safety and Health Administration in the USA showed the median dust exposure to be 1.20 mg/m^3; 90% of all exposures were <2.78 mg/m^3 (National Institute for Occupational Safety and Health, 1979).

Before the adoption of technical preventive measures in 1950, exposures in the talc operation in the Germanasca and Chisone Valley (Piedmont), Italy, were reported to be approximately 800 mppcf [~28 250 particles/cm^3] in the mines and 25 mppcf [~883 particles/cm^3] in the mills. Exposures in both areas were reduced to less than 10 mppcf [~353 particles/cm^3] after 1965 when improved ventilation techniques and wet drilling procedures were introduced. Mineralogical analyses of the footwall rocks demonstrated that they contained quartz, muscovite, chlorite, garnet, calcite, magnesite and small quantities of other minerals. In a few specimens of footwall rocks, a small amount of tremolite was detected, but no other type of amphibole or chrysotile. Talc specimens from these mines were found very commonly to contain chlorite, but no amphibole or chrysotile minerals. The quartz content of powdered talc specimens was generally below the detection limits of X-ray diffraction (Rubino *et al.*, 1976). In recent years, the mean exposure to respirable dust was 1.1 mg/m^3 (range, 0.5–2.5 mg/m^3), while the mean exposure to talc alone was 1.0 mg/m^3 (range, 0.3–2.0 mg/m^3). The authors stated that there was a remarkable difference in the amount of quartz in air dust in mines and mills and within jobs in the mine between drilling and other occupations. This was mainly due to the high content of quartz in footwall rocks, rather than to the absence of quartz particles in talc minerals (Coggiola *et al.*, 2003). [The Working Group noted that the analytical methods were not described in detail and the mineral habit of the tremolite was not documented.]

Wild *et al.* (1995) reported on a survey of the respiratory health of workers in a French talc producing factory. At this quarry, crude talc was extracted and transported directly to the mill using an overhead cable. The extracted ore consisted of a mixture of talc, chlorite, some dolomite (<3%), occasionally quartz (<3%) and traces of calcite, apatite, pyrite and mica. Amphiboles were not detected. A total of 1440 personal samples were taken between 1986 and 1991. The mean levels of exposure to respirable dust ranged from 0.5 mg/m^3 for secretaries, managerial staff and outdoor workers who handled the railway wagons to 15 mg/m^3 for site cleaning staff. In 1991, only one exposure group of four maintenance workers was estimated to have a mean exposure in excess of 5 mg/m^3. However, the probability of exceeding an exposure level of 5 mg/m^3 was more than 10% for most maintenance and some production workers. This was explained by the high variability of exposure among maintenance workers; eight of 10 groups of workers in the maintenance workshop had geometric standard deviations >3. Exposure was found to be more homogeneous among the production workers. The authors claimed that the introduction of centralized aspiration devices and new working procedures had resulted in lower levels of exposure. Mean levels of exposure in the in the past were estimated to have been up to 60 mg/m^3, especially for workers storing jute bags of talc in wagons. Before 1985, the highest levels of exposure to dust for site cleaning staff were estimated to be 30 mg/m^3; for sacking and drying, exposure levels in the workplace before 1975 were estimated to be 20 mg/m^3.

Wild *et al.* (2002) also provided some additional exposure information for three Austrian mines and their respective mills in the Styrian Alps. The ore mined at one site

(site B) consisted of a talc–chlorite mixture with gange [dead rock] inclusions of about 25% (mainly alumino-silicate rock). The gange was dumped in the mine so that the milled product was talc–chlorite and contained between 0.5 and 4% quartz. At site C, the material mined was a talc–dolomite aggregation with a medium talc content of 25%. The amount of quartz in the end-product was below 1%. However, materials from certain parts of this mine that were rich in dolomite could have contained 2–3% quartz. At site D, a light greyish quartz–chlorite–mica schist (alumino-silicate rock that consisted of an aggregation of more or less equal proportions of mica, chlorite and quartz) was mined and milled. Analyses of dust from the lungs and lymph nodes of employees in the Austrian talc industry confirmed the presence of quartz and the absence of amphibole and serpentine (Friedrichs, 1987). Table 1.11 summarizes the levels of exposure reported in the French and Austrian talc mines and associated mills.

Table 1.11. Levels (mg/m^3) of exposure to respirable dust in one French and two Austrian talc mines and associated mills

Exposure group	Occupation	Mine/mill	No. of samples	Mean	Range	Date
No exposure	Office workers	French talc quarry	168	0.2		1986
Low exposure (<5 mg/m^3)	Maintenance workers, garage mechanics, production workers with dust control/LEV	French talc quarry	100	0.5–2.6	0.11–17	1986
		Austrian mine B	173		0.02–4.61	1988–92
		Austrian mine C	33		0.02–4.1	1991–92
Median exposure (5–30 mg/m^3)	Recent production workers	French mine A	193	3.5–25.6	0.21–134	NR
		Austrian mines B and C	17		6.5–19.6	NR
High exposure (>30 mg/m^3)	Milling, maintenance, cleaning	Austria	3		73–159	End of 1980s

From Wild *et al.* (1995, 2002)
LEV, local exhaust ventilation; NR, not reported

Several samples were collected from a crushing, grinding and talcum powder packing unit at a plant in Pakistan to measure different particle sizes (Jehan, 1984). In total, seven 1-hour samples were collected, one for total suspended particles (concentration, 6.14 mg/m^3), one for particulate matter (PM) <10 μm (1.12 mg/m^3), one for PM <7 μm (1.93 mg/m^3), one for PM <5 μm (0.40 mg/m^3), one for PM <3 μm (0.26 mg/m^3), one for

PM <2 μm (0.05 mg/m^3) and one for PM >1 μm (1.55 mg/m^3). Further analyses of the samples with PM <10 μm and <2 μm by scanning electron microscopy showed that the fibre concentration was 0.25 fibres/cm^3 and 0.12 fibres/cm^3, respectively. Analyses by polarized light microscopy indicated the presence of asbestiform tremolite, chrysotile and anthophyllite in these samples.

(b) User industries

Only limited information is available on exposures in secondary industries in which talc is used or processed further. Results from some surveys are summarized in Table 1.12.

Table 1.12. Mineral composition of talc used for dusting in the rubber industry in the USA

Reference	Location	Date	Mineral composition	Method of analysis
Hogue & Mallette (1949)	Vermont	1943–48	Stated to be 'pure talc'	Impinger
Dement & Shuler (1972)	Canton, MA	1972	2–3% quartz	Gravimetric, optical fibre counts
Fine *et al.* (1976)	Vermont	1972–74	Trace of quartz (<1%), <2 fibres/cm^3	Gravimetric

Personal air samples collected in a rubber band production plant, where housekeeping, ventilation and work practices were poor and talc was used as an anti-sticking agent, had time-weighted average (TWA) concentrations of respirable dust of 2.5–7.8 mg/m^3 (average, 4.8 mg/m^3) for extruders, 5.3 and 6.1 mg/m^3 for vulcanizers and 0.9 and 1.3 mg/m^3 for cutters. Exposures to total dust were found to range from 5.4 to 199 mg/m^3. The talc was reported to contain 2–3% quartz. Within these exposures, 4.7–19.2 fibres were >5 μm/cm^3 as measured by phase-contrast optical microscopy (Dement & Shuler, 1972). [The Working Group noted that no electron microscopic analysis was conducted to confirm the identity of the fibres; however, most of these were probably not asbestos.]

Concentrations of respirable dust in two rubber manufacturing plants where Vermont talc was used as an anti-sticking agent are shown in Table 1.13. Eighteen of 21 samples analysed for quartz contained less than 1% by weight. In 12 samples analysed for fibres, using phase-contrast microscopic techniques for asbestos, all concentrations were less than 2 fibres/cm^3. No electron microscopic fibre analysis was reported (Fine *et al.*, 1976). Hogue and Mallette (1949) found an average dust concentration of 15–50 mppcf [~530–1765 particles/cm^3] talc in two rubber plants that used Vermont talc. Average exposures were 20 mppcf [~706 particles/cm^3] for tube machine operators, 35 mppcf

[1236 particles/cm^3] for tube 'bookers', 15 mppcf [~530 particles/cm^3] for tube cure men and 50 mppcf [~1765 particles/cm^3] for 'line rerollers'.

Table 1.13. Concentrations of respirable dust in rubber processing plants that used talc

Location	No. of samples	Average dust concentration (mg/m^3)
Plant A		
Lorry and bus inner tubes (splicer)	7	0.60
Lorry and bus inner tubes (cureman)	6	1.41
'Tuber operator'	3	0.47
'Booker'	3	0.74
Farm service inner tubes (splicer)	6	0.82
Farm service inner tubes (cureman)	2	0.91
Plant B		
Rubber band area	6	3.55
Gum engraving room	6	0.64
Hose extruding	4	0.51
Curing heavy duty flaps	3	1.29
'Dust room'	2	0.59

From Fine *et al.* (1976)

In a mortality study of lung cancer and respiratory disease among pottery workers exposed to silica and talc, Thomas and Stewart (1987) estimated exposure to non-asbestiform talc and tremolitic talc. Exposure to talc occurred almost exclusively in the cast shop. Montana steatite talc that had been used to dust moulds since 1955 appeared to contain no asbestiform talc (Gamble *et al.*, 1982; Grexa & Parmentier, 1979). However, before 1955, flint and ground clay had been used to dust the moulds. Up to 1976, tremolitic talc had been used in some glazes. No measurements of airborne talc or silica were available, and exposure estimates were based on detailed knowledge of industrial processes and job duties. All exposures to talc were associated with high exposure to quartz from the clays. Quartz particles from clay are smaller than approximately 4 μm.

Kauppinen *et al.* (1997) developed an international database of exposure measurements in the pulp, paper and paper product industries. In total, 63 measurements for talc were included in this database—four measurements in the pulp production and 59 in paper or paperboard production and recycling; 6% of the samples exceeded the 8-hour TWA threshold limit value (TLV) for talc of 2 mg/m^3 respirable dust (ACGIH® Worldwide, 2005). [No information was provided on the methods of measurement, the time period when these measurements were taken or the actual processes and the materials used during these measurements. As only a limited number of measurements were available, it is improbable that these results are representative of exposure to talc in this industry.]

Kauppinen *et al.* (2002) described the prevalence of exposure to talc among workers in the on-machine coating of paper. In total, 25 departments were assessed: in 60% of the departments, more than 5% of the workers were exposed to talc, with a median prevalence of exposure of 51–90%. The median level of exposure was assessed as medium (0.6–2 mg/m^3) by a team of occupational hygienists.

Pooley and Rowlands (1975) examined talc imported into the United Kingdom. These talcs were used in a variety of industries, including cosmetics. Only one of the samples examined contained tremolite (>30%). [The number of samples examined and their use were not given. The electron micrograph of the sample identified as tremolite and the concentration of tremolite are consistent with the Gouverneur District New York State talc, which is unlikely to have been used in cosmetics.] All other elongated particles detected in the samples were identified as laths or rolled sheets of talc, chlorite or sepiolite (several samples).

1.3.3 *Consumer exposure*

(a) Mineralogical characterization

Two studies that were conducted between 1968 and 1977 examined the mineralogy of consumer talc in the USA.

Cralley *et al.* (1968) examined 22 cosmetic talc products that were purchased off the shelf for particles >5 μm with a 3:1 or greater aspect ratio (diameter:length) and found that on average 19% of the particles met these dimensional criteria. [No additional information was provided on the source of the talc products, but the Working Group noted that the authors were located in Cincinnati, OH, USA.] The authors concluded that these 'fibres' were predominantly talc, but suggested that some may have been anthophyllite, tremolite, pyrophyllite or chrysotile. [The Working Group noted that no data were provided to support this statement. The statement was based only on the fact that these minerals have been reported to occur in some talc deposits.] Using X-ray diffraction, quartz was found at a level of 0.2–53.4% in these samples. No limit of detection was given, but the lowest concentration reported was 0.2 wt%. Analysis for other minerals was not carried out.

Rohl *et al.* (1976) examined 20 body powders, baby powders and facial talcums and one pharmaceutical talc, all of which were purchased at retail stores in New York City between 1971 and 1975. Based on X-ray diffraction, optical microscopy and transmission electron microscopy, the concentration of tremolite, anthophyllite and quartz was estimated and the presence of several other minerals was established (see Tables 1.14 and 1.15). One of the 21 samples was composed entirely of cornstarch and one contained primarily pyrophyllite and only a small amount of talc. Quartz was present in nine of the 21 samples, tremolite was reported in nine, anthophyllite in seven and serpentine in two samples. Chrysotile was confirmed by transmission electron microscopy in these samples, but no estimates of the concentrations were provided. Krause (1977), in a review of this study, pointed out that the overlap of the X-ray diffraction patterns of tremolite and

anthophyllite makes accurate estimation of their concentration by this method impossible. A similar problem was pointed out for estimates of the concentration of quartz because of overlap with several talc peaks. [The Working Group believed that these criticisms were reasonable and that little reliance can be placed on the reported concentration of tremolite or anthophyllite. The Working Group also noted that Rohl *et al.* (1976) stated that their methodology did not distinguish between asbestos and non-asbestiform mineral fragments. In addition, the representativeness of these samples for other countries or for other areas of the USA is unclear.]

Table 1.14. Concentrations of minerals in 20 samples of body powders, baby powders and facial talcums and one sample of pharmaceutical talc

Mineral	No. of samples	Concentration range (wt%)
Quartz	9	1.6–35.1
Tremolite[a]	9	0.1–10.3
Anthophyllite[a]	7	2.1–11.4
Chrysotile	2	<0.5[b]

From Rohl *et al.* (1976)
[a] Six samples containcd both minerals, which resulted in uncertainty about the absolute concentrations given for each mineral.
[b] Visual estimates by transmission electron microscopy were given as 0.25–0.5%, but no methodology was provided.

Table 1.15. Qualitative measurements of minerals other than anthophyllite, chrysotile, quartz or tremolite in 20 samples of body powders, baby powders and facial talcums and one sample of pharmaceutical talc

Mineral	No. of samples in which the mineral was present
Talc	20[a]
Chlorite	16[b]
Calcite	8[b]
Phlogopite	3[b]
Pyrophillite	2[b]
Dolomite	1[b]
Kaolin	1[b]

From Rohl *et al.* (1976)
[a] Talc was the major mineral in 19 of the 20 samples.
[b] Present in quantities above trace amounts

Paoletti *et al.* (1984) examined talc powders that were used in pharmaceutical and cosmetic preparations. Tremolite was identified in two of six cosmetic talcs on the Italian market. Six of 14 samples provide by the European Pharmacopoeia contained either tremolite, anthophyllite or chrysotile. [No information was provided on the concentration of minerals, including tremolite and quartz, or on the time of purchase.]

Jehan (1984) reported on commercial cosmetic-grade talc (baby and body talcum powder) used in Pakistan between 2000 and 2004. Sixty samples were analysed using atomic absorption techniques, X-ray diffraction, polarized light microscopy and scanning electron microscopy, and the presence of asbestiform chrysotile, both asbestiform and non-asbestiform tremolite and anthophyllite was identified. Asbestiform varieties of tremolite and anthophyllite were uncommon, while chrysotile was common. Respirable quartz was also identified in most (80%) of the samples.

Some products listed by the Cosmetic and Toiletries Formulations Database are shown in Table 1.7. Listing is voluntary and may not be representative of products that are on the market. Tables 1.16 and 1.17 present the average mineral composition of commercial products that were sold under the name of talc in North America and Europe, respectively, in the late 1980s.

(b) Use of talc for feminine hygiene

The use of body powder for feminine hygiene can be estimated from the prevalence reported for controls in case–control studies that investigated the association between the use of cosmetic talc for feminine hygiene and the risk for ovarian cancer.

The prevalence of ever use in these studies is summarized in Table 1.18. Higher prevalences were generally reported in studies from Canada, the United Kingdom and the USA (up to 59%), whereas the lowest prevalences were generally reported in studies conducted in other countries, including China, Greece and Israel (2.2–5.6%).

Studies with high prevalences also reported doses in terms of frequency, duration of use, age at first use or cumulative doses. Frequency of use may vary from a few times per month to more than once a day, and a large proportion of use is more or less daily. Duration of use ranges up to more than 40 years. The cumulative exposure to talc by perineal dusting was over 10 000 days in 4% of the users in one study (Cook *et al.*, 1997). The use of talcum powder for feminine hygiene is acquired in young adulthood, since 80% of women who use body powder start before the age of 25 years (Harlow & Weiss, 1989).

The types of application also vary. Body powder can be applied perineally, on napkins or on underwear. Dusting of the perineum after bathing appears to be the most frequent single type of application, but simultaneous uses have also been reported. Alternatively, exposure may occur as a result of storing a diaphram in body powder or contamination from the male partner who has used body powder. One study in the USA reported that the use of deodorant spray had a prevalence of 24% (Cook *et al.*, 1997).

In several of the studies in Table 1.18, the interviews on powder use occurred before 1988. Of these, all but one were conducted in the USA. Information on the composition

Table 1.16. Average mineralogical composition (%) of commercial products sold under the name of talc in North America

	Canada			Vermont				California	Texas	Montana		New York
Talc production (thousand tonnes)	40 floated	10	30	70	30 floated	200	12 floated	10	307	326	20	140
Mineral (%)												
Talc	92.5	64.5	60.5	55	90	52.5	94.5	54	80	94	8	25
Chlorite	3	11.5	10.5	7	7	9	1.5	5	1	4.5	85.5	
Dolomite	1	4	8	2	0.5	2	0.5	9	12.5	0.5	0.5	
Magnesite	1.5	17	18	34	2	33.5	0.5	16		T	T	
Serpentine			T									25
Quartz									T	T	T	
Mica	T	T							T	T	T	
Calcite	T											
Tremolite												44
Anthophyllite												5

From Ferret & Moreau (1990)
T, identified mineral that could not be measured by the methods of analysis used

Table 1.17. Average mineralogical composition (%) of commercial products sold under the name of talc in Europe

	Finland		Sweden	Norway	United Kingdom	France	Austria	Italy				Spain		
Talc production (thousand tonnes)	75 floated	250 floated	15	50	17	320	80	20	40	46	17	33	20	28
Mineral (%)														
Talc	93	88	64	55	54	59	51.5	51.5	86	51	47	89	80.5	53
Chlorite	3.5	8.5	16.5	11	9	39	42	43	9.5	19.5	22.5	6	12	18.5
Dolomite	0.5	T	11.5	2	2	1.5	1	2	1.5	12	14.5	2	1.5	6
Magnesite	1.5	2		29	30.5		1		0.5	10	14.5			18.5
Serpentine										T	T			
Quartz			T	T	T		T	T		T			T	
Mica			T				T	T				1.5	1.5	
Calcite			T	T				T		T		0.5	T	
Tremolite			T											

From Ferret & Moreau (1990)
T, identified mineral that could not be measured by the methods of analysis used.

Table 1.18. Assessment of exposure to body powders in the perineal area by women

Location	No. of controls	Prevalence of ever use of talc	Type of perineal use of powder by women	Reference
Massachusetts, USA	215	28.4%	Exposure to talc by dusting	Cramer *et al.* (1982)
Washington DC, USA	171	1.8%	Body talc	Hartge *et al.* (1983)
California, USA	539	45.8%	Use of talcum powder	Whittemore *et al.* (1988)
United Kingdom	451	59.0%	Use of talc	Booth *et al.* (1989)
Washington, USA	158	40.5%	Exposure to powder (cornstarch, baby powder, talc, deodorizing powder); detailed information on type of powder used	Harlow & Weiss (1989)
Massachusetts, USA	239	39.3%	Exposure to baby powder, deodorizing or scented powder	Harlow *et al.* (1992)
China	224	2.2%	Dusting powder	Chen *et al.* (1992)
Maryland, USA	46	17.3%	Genital bath talc (also asked use on napkins or diaphragm)	Rosenblatt *et al.*(1992)
Athens, Greece	193	3.6%	Local application of talc	Tzonou *et al.* (1993)
Israel	408	5.6%	Use of talc	Shushan *et al.* (1996)
Toronto, Canada	564	35.6%	Regular application of talc	Chang & Risch (1997)
Washington, USA	422	39.3%	Dusting with cornstarch, talcum powder, baby or scented powder, and deodorizing spray	Cook *et al.* (1997)
New York, USA	50	26%	Use of talc	Eltabbakh *et al.* (1998)
Montreal, Canada	170	4.7%	Use of talc	Godard *et al.* (1998)
New England, USA	523	18.2%	Use of talc, baby or deodorizing powders or cornstarch	Cramer *et al.* (1999)
New York, USA	693	35%	Use of talc (on genital or thigh area and sanitary napkins)	Wong *et al.* (1999)
Delaware Valley, USA	1367	40%	Use of talc (on genital/rectal area and feet, sanitary napkins, underwear, diaphragm/cervical cap, male partner user)	Ness *et al.* (2000)
California, USA	1122	37.1%	Use of talcum powder	Mills *et al.* (2004)
USA	78 630 cohort	40.4%	Use of talc	Gertig *et al.* (2000)

of baby powder, body powder, facial powder and pharmaceutical talcum powder on the market in New York City before 1976 suggests that many of these products were impure and contained anthophyllite, carbonate, chlorite, chrysotile, phlogopite, pyrophyllite, quartz and tremolite (Cralley *et al.*, 1968; Rohl *et al.*, 1976). After 1976, these powders probably did not contain anthophyllite, chrysotile or tremolite but may have contained up to 10% of other minerals including carbonate, chlorite and quartz (Grexa & Parmentier, 1979). In 1994, baby talcum powder available in the USA typically contained 99% talc; body powder typically contained 65–70% talc and the remaining material was cornstarch, sodium bicarbonate and fragrance (Zazenski *et al.*, 1995).

(c) Other uses of cosmetic talc

Russell *et al.* (1979) and Aylott *et al.* (1979) reported exposure to respirable dust during the use of talcum powders on the face, body and babies. Russell *et al.* (1979) took 48 measurements during baby dusting operations and 44 measurements during the application of powders to adult bodies. Adult exposure was assessed during normal face/body powdering practices by placing cyclone samplers on shelves at an appropriate height or by positioning a cyclone attached to a headband near the nose (i.e. in the breathing zone). Exposure to respirable dust was 2.03±1.48 mg/m^3 during adult application and was estimated to be 0.19 mg/m^3 for babies. The estimated duration of the application was 1.23 minute for adults and 0.52 minute for babies.

Aylott *et al.* (1979) measured levels of exposure to respirable dust during the application of loose face powder (24 measurements), adult dusting powder (43 measurements) and baby dusting powder (32 measurements). In the study of baby dusting powder, a doll was used. The exposure to respirable dust during face powdering ranged from <0.1 to 1.7 mg/m^3 (duration, 10–25 seconds), that for adult dusting powder ranged from 0.2 to 3.3 mg/m^3 (duration, 15–80 seconds) and that for baby powders ranged from <0.1 to 0.9 mg/m^3 (duration, 15–60 seconds).

(d) Other exposures

Talc is used as a surface lubricant on the majority of condoms manufactured; contact with condoms may also represent a direct means of exposure of the female genital tract to talc (Kasper & Chandler, 1995).

Exposure to talc can also occur during surgical procedures when using powdered gloves. Talc particles were observed in the navels of small children, in the testes, on the vocal cords, in the urinary bladder tract and after removal of varicous veins (Ramelet, 1991; Simşek *et al.*, 1992). During breast implantations, it is possible that talc from surgical gloves can lead to unwanted encapsulation (Chandler & Kasper, 2003).

1.3.4 *Environmental exposure*

Talc is often detected as a common anthropogenic contaminant in suspended sediment, even in remote snowfields in the Alps; this has been ascribed to its emission

into the atmosphere by industrial and agricultural process (Hillier, 2001). Talc had also been identified in the sediment of the River Don in Scotland (United Kingdom), although no obvious industrial or agricultural sources of the talc were apparent (Hillier, 2001).

1.4 Regulations and guidelines

Occupational exposure regulations and guidelines for talc in several countries are presented in Table 1.19.

Table 1.19. Occupational exposure standards and guidelines for talc

Country or region	Concentration (mg/m^3)	Interpretation	Carcinogenicity
Australia	2.5	TWA	
Belgium	10 (I)	TWA	
	2	TWA	
China	3 (T)	TWA	
	4	STEL	
Canada			
Alberta	2 (R)	TWA	
British Columbia	2 (R)	TWA	
Ontario	2 fibres/cm^3 (R)	TWA; value is for particulate matter containing <1% crystalline silica	
Quebec	3 (R)	TWA (talc–containing no mineral or asbestos fibres)	
Czech Republic	10 (R)	TWA; fibres >5%	
	2 (R)	TWA; fibres ≤5%	
	10 (T)	TWA	
Denmark	0.3 fibres/cm^3	TWA; containing fibres	K
Finland	5	TWA	
Germany	(R)	MAK; without asbestos fibres	3B
Hong Kong	2 (R)	TWA	A4
Ireland	10 (I)	TWA	
	0.8 (R)	TWA	
Japan	0.5 (R)	TWA	
	2 (T)	TWA	
Malaysia	2 (R)	TWA	
Mexico	2 (R)	TWA	A4
Netherlands	1 (R)	TWA	
New Zealand	2 (R)	TWA	
Norway	2 (R)	TWA	
	6 (T)	TWA	

Table 1.19 (contd)

Country or region	Concentration (mg/m^3)	Interpretation	Carcinogenicity
Poland	1 (R)	TWA	
	4 (I)	TWA	
South Africa	1 (R)	TWA	
	10 (I)	TWA	
Spain	2 (R)	Ceiling; containing no asbestos fibres and <1% crystalline silica	
Switzerland	2	TWA	
United Kingdom	1 (R)	TWA	
USA			
ACGIH (TLV)	2 (R)	TWA; containing no asbestos and <1% crystalline silica	A4
NIOSH (REL)	2 (R)	TWA (10-h)	
OSHA (PEL)	~3 (20 mppcf)	TWA; containing <1% quartz	

From Direktoratet for Arbejdstilsynet (2002); Työsuojelusäädöksiä (2002); SUVA (2003); ACGIH® Worldwide (2005); Deutsche Forschungsgemeinschaft (2005); Health and Safety Executive (2005)
ACGIH, American Conference of Governmental Industrial Hygienists; I, inhalable dust; MAK, maximum concentration in the workplace; mppcf, millions of particles per cubic foot; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; R, respirable dust; REL, recommended exposure limit; T, total dust; STEL, short-term exposure limit; TWA, 8-h time-weighted average (unless otherwise specified)
[a] 3B, substances for which in-vitro test, or animal studies have yielded evidence of carcinogenic effects that is not sufficient for classification of the substance in one of the other categories; K, included in the list of substances considered as carcinogenic; A4, not classifiable as a human carcinogen

The Food and Drug Administration regulates talc in the USA, and states that it is generally recognized as safe for use in colour additives in foods, drugs and cosmetics, and in paper, paper products, cotton and cotton fabrics that come into contact with food. The Food and Drug Administration also states that talc is present in over-the-counter astringent drug products (National Toxicology Program, 2000).

The Food Chemical Codex (2003) provides specifications for food-grade talc, including the statement that "talc derived from deposits that are known to contain associated asbestos is not food grade." Under the voluntary guidelines initiated in 1976, the Cosmetic, Toiletry, and Fragrances Association stated that all cosmetic talc should contain at least 90% platy talc (hydrated magnesium silicate) that is free from detectable amounts (<0.5%) of fibrous, asbestos minerals (Gilbertson, 1995; Zazenski *et al.*, 1995; National Toxicology Program, 2000).

The current Occupational Safety and Health Administration (2005) permissible exposure level for non-asbestiform talc in the USA is ~3 mg/m^3 (20 mppcf) measured as respirable dust. The current American Conference of Governmental Industrial Hygienists TLV-TWA is 2 mg/m^3 (15 mppcf), which also is the proposed Occupational Safety and Health Administration limit. Levels of exposure of workers may exceed three times the TLV-TWA for no more than 30 minute during the workday (National Toxicology Program, 2000).

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2. Studies of Cancer in Humans

2.1 Occupational exposure

2.1.1 *Talc miners and millers* (Table 2.1)

Rubino *et al.* (1976) conducted a study of mortality among men who had begun work in the mines and mills of a talc operation in the Germanasca and Chisone valleys (Piedmont), Italy, between 1921 and 1950 and who had been employed for at least 1 year in a job that involved exposure to talc. A total of 1514 miners and 478 millers were identified, of whom 168 miners (11.1%) and 40 millers (8.4%) were lost to follow-up before the end of the study in June 1974, yielding a combined cohort of 1784 men (89.6%) for analysis. The talc from these mines was described as pure and was reported to have been used in the pharmaceutical and cosmetics industries. However, due to the presence of 'footwall contact rocks' and rock-type inclusions in the mines, drilling operations were associated with exposure to dusts that contained high levels of silica; such inclusions were removed before milling and talc products were reported to have a content of free silica below 2%. [The Working Group understood that the term 'silica' was in fact quartz.] In a few instances, talc samples from the area showed small amounts of tremolite when examined by X-ray diffraction, but no amphibolic asbestos or chrysotile were detected. For each worker, cumulative exposure was estimated from regular measurements of respirable dust content in the air of mines and mills during the period 1948–74 and individual work histories were abstracted from files of the mining company. Periods of time during which the dust level was assumed to be uniform were first selected and cumulative exposure was then calculated as the summed product of the number of years in each specific working period (years) and the associated dust levels (million particles per cubic foot; mppcf), resulting in an overall measure of mppcf–years. Once individual cumulative exposures had been assigned, miners and millers were then classified separately into low, medium and high levels of exposure. Ranges of exposure (mppcf–years) for miners were 566–1699, 1700–5665 and 5666–12750, respectively; ranges of exposure for millers were 25–141, 142–424 and 425–906, respectively. For each of the 1784 workers included (1346 miners and 438 millers), one unexposed control subject was chosen at random from among male inhabitants of a nearby small, rural town. The control was matched to the talc worker on year of birth and vital status at date of entry into the study [date not specified]. Cause of death for 885 (95.1%) of 931 deceased workers and 1067 (94.8%) of 1126 deceased controls was obtained from regional death certificate files supplemented with information from relatives, physicians and medical records. Observed numbers of deaths among talc workers were compared with expected numbers, calculated by the use of age-specific mortality rates experienced by the control cohort. The standardized mortality ratio (SMR) for all causes combined was 0.9 (95%

Table 2.1. Cohort studies of mortality from and incidence of cancer in populations occupationally exposed to non-asbestiform talc

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Rubino *et al.* (1976), Germanesca and Chisone valleys (Piedmont), Italy	1992 male talc workers (1514 miners, 478 millers) employed >1 year in talc-exposed job during 1921–1974; hired 1921–1950; mortality follow-up, 1921–74; vital status, 90%; cause of death: 95% of exposed workers, 95% of controls	Occupational history from plant records; respirable dust measurements, 1948–1974; quantitative estimation of cumulative exposure for individual workers, expressed as summed product of duration (years) and exposure (million particles per cubic foot, mppcf); classification of workers into 3 levels of exposure	All cancers			**SMR**	
				All miners	100	0.8 (0.6–0.9)	Adjusted for age; comparison with unexposed, age-matched controls from neighbouring rural town; controls matched on vital status at date of entry into study; miners and millers exposed to a very pure form of talc; miners also exposed to inhalable silica; significantly elevated SMRs for silicosis with and without tuberculosis among miners; estimates increased with increasing cumulative exposure; no observed cases of mesothelioma; no smoking data for exposed workers or unexposed controls
				All millers	42	0.9 (0.7–1.2)	
				Miners (mppcf–years)			
				Level 1: 566–1699	38	1.2 (0.8–1.6)	
				Level 2: 1700–5665	28	1.0 (0.7–1.4)	
				Level 3: 5666–12750	34	0.9 (0.6–1.2)	
				Millers (mppcf–years)			
				Level 1: 25–141	18	1.1 (0.2–3.2)	
				Level 2: 142–424	13	1.3 (0–2.9)	
				Level 3: 425–906	11	0.7 (0.4–2.7)	
			Lung, bronchus and trachea	All miners	9	0.5 (0.2–0.9)	
				All millers	4	0.6 (0.2–1.6)	
				Miners (mppcf–years)			
				Level 1: 566–1699	3	1.1 (0.6–1.7)	
				Level 2: 1700–5665	1	0.5 (0.7–2.3)	
				Level 3: 5666–12750	5	1.1 (0.4–1.3)	
				Millers (mppcf–years)			
				Level 1: 25–141	3	1.7 (0.3–4.9)	
				Level 2: 142–424	1	1.25 (0–7.0)	
				Level 3: 425–906	0	–	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Rubino *et al.* (1979), Germanesca and Chisone valleys (Piedmont), Italy	1678 male talc workers (1260 miners, 418 millers); mortality follow-up, 1946–74	Same exposure categories as Rubino *et al.* (1976)	Lung			**SMR**	Re-analysis of cohort reported in Rubino *et al.* (1976); SMRs recalculated using national death rates instead of comparison with neighbouring rural population; national death rates available only from 1951 onward; rates for 1951 were applied for 1946–50
				All miners	8	0.5 (0.2–0.9)	
				All millers	4	0.7 (0.2–1.7)	
				Miners (mppcf–years)			
				Level 1: 566–1699	2	0.5 (0–1.9)	
				Level 2: 1700–5665	1	0.2 (0.5–1.2)	
				Level 3: 5666–12750	5	0.6 (0.2–1.4)	
				Millers (mppcf–years)			
				Level 1: 25–141	3	2.0 (0.4–5.8)	
				Level 2: 142–424	1	0.7 (1.7–3.7)	
				Level 3: 425–906	0	–	
Selevan *et al.* (1979), Vermont, USA	392 white male talc workers (163 miners, 225 millers) employed >1 year between 1940 and 1969; mortality follow-up: date of first radiogram, 12-month employment anniversary or January 1940, whichever was later; follow-up through 1975; vital status: 99%; cause of death: 94%	Historical insufficient information to calculate cumulative exposure histories; cohort classified into two work areas: mining and milling.				**SMR**	Adjusted for age, sex, race, calendar year; US death rates: 1940–67; linear extrapolation for all causes of death: 1967–69. Vermont death rates for specific causes of death: 1949–75; workers selected from annual radiographic survey of dusty trades; no data on smoking habits for millers or miners; exposure to radon daughters in mine; radiographic evidence of pneumoconiosis in most workers who died from non-malignant respiratory disease
			All causes	Total cohort	90	1.2 [0.9–1.4]	
				Millers	44	1.2 [0.9–1.6]	
				Miners	34	1.3 [0.9–1.8]	
			All cancers	Total cohort	16	[1.3 (0.7–2.0)]	
				Millers	5	[0.8 (0.3–1.9)]	
				Miners	7	[1.7 (0.7–3.5)]	
			Respiratory cancer	Total cohort	6	[1.6 (0.6–3.5)]	
				Millers	2	[1.0 (0.1–3.7)]	
				Miners	5	[4.3 (1.4–10.1)]	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wergeland *et al.* (1990), northern and western Norway	389 male talc-exposed workers (94 miners, 295 millers) employed >1 year in mine (1944–72) or >2 years in mill (1935–72); mortality and cancer incidence follow-up; 1953–87	Subjective assessment of exposure by experienced colleagues; workers classified by total duration of employment in jobs with low, medium, high and unknown exposure				**SMR**	Adjusted for age, smoking (miners only); national death rates: 1953–87; main minerals in mined talc deposit were talc and magnesite; 90% of raw material for mill from mine; 10% from India; no information on smoking habits for millers; smoking habits for miners above national average; low levels of exposure to radon daughters
			All causes	*Total cohort*	117	0.8 (0.6–0.9)	
				Miners	27	[0.8 (0.5–1.2)]	
				Millers	90	[0.7 (0.6–0.9)]	
			All cancers	*Total cohort*	26	0.8 (0.5–1.1)	
				Miners	9	[1.3 (0.6–2.5)]	
				Millers	17	[0.6 (0.4–1.0)]	
						SIR	
			All cancers	*Total cohort*	46	0.9 (0.7–1.2)	
				Miners	15	[1.4 (0.8–2.3)]	
				Millers	31	[0.8 (0.5–1.1)]	
				Years employed			
				1–4	11	[1.1 (0.6–2.1)]	
				5–19	19	[0.8 (0.5–1.2)]	
				>20	16	[0.9 (0.5–1.5)]	
				Years since first employment			
				1–19	6	[0.4 (0.2–0.9)]	
				20–29	18	[1.1 (0.7–1.8)]	
				>30	22	[1.1 (0.7–1.6)]	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wergeland *et al.* (1990) (contd)			Lung	*Total cohort*	6	0.9 (0.3–2.0)	
				Miners	2	[1.6 (0.2–5.7)]	
				Millers	4	[0.8 (0.2–2.0)]	
				Years employed			
				1–4	0	–	
				5–19	3	[1.0 (0.2–3.0)]	
				>20	3	[1.0 (0.2–3.0)]	
				Years since first employment			
				1–19	2	[1.1 (0.1–4.1)]	
				20–29	1	[0.5 (1.3–2.8)]	
				>30	3	[1.1 (0.2–3.2)]	
			Stomach	*Total cohort*	6	1.1 (0.4–2.2)	
				Miners	3	[2.5 (0.5–7.4)]	
				Millers	3	[0.7 (0.1–2.1)]	
				Years employed			
				1–4	2	[2.0 (0.2–7.2)]	
				5–19	2	[0.8 (0.1–2.6)]	
				>20	2	[1.2 (0.1–4.3)]	
				Years since first employment			
				1–19	1	[0.6 (1.4–3.1)]	
				20–29	2	[1.1 (0.1–4.0)]	
				>30	3	[1.7 (0.3–4.8)]	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wild (2000), Luzenac, France	1160 talc workers (1070 men, 90 women) actively employed in 1945 or hired during 1945–94 and employed >1 year; mortality follow-up,,1945–96; vital status: 97%; cause of death: 74% pre-1968 and 98% post-1968	Exposures assessed for case–control study; semi-quantitative, site-specific job-exposure matrix based on personal dust measurements (1986 onwards) and subjective assessments by experienced workers; workers assigned to four categories of exposure: no exposure, ambient (<5 mg/m^3), medium (5–30 mg/m^3) and high (>30 mg/m^3); exposure prior to hiring also coded: none, probable exposure to quartz, certain exposure to quartz, exposure to other carcinogens.		*Male talc workers*		**SMR**	Adjusted for age, sex, smoking, prior exposure to quartz (case–control study only); partial overlap of study population with Leophonte *et al.* (1983) and Leophonte and Didier (1990); extent of overlap unknown; national mortality rates applied: pre- and post-1968; regional mortality rates applied: post-1968: excess mortality from lung cancer disappeared when national rates applied
			All causes	Pre-1968 (national rates)	101	0.8 (0.6–1.0)	
				Post-1968 (national rates)	294	0.8 (0.7–0.9)	
				Post-1968 (regional rates)	294	0.9 (0.8–1.0)	
			All cancers	Post-1968 (regional rates)	80	1.0 (0.8–1.3)	
			Lung	Post-1968 (regional rates)	21	1.2 (0.8–1.9)	
				Post-1968 (national rates)	21	0.9 (0.6–1.4)	
				Men <60 years of age	7	2.0 [0.8–4.0]	
				Latency period <20 years	5	2.4 [0.8–5.6]	
				Duration of employment <10 years	8	2.1 [0.9–4.1]	
			Stomach	Post-1968 (national rates)	5	1.2 (0.4–2.8)	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wild (2000) (contd)	Nested case–control study: lung cancer, non-malignant pulmonary disease and stomach cancer; three randomly selected controls per case; lung cancer: 23 cases, 67 controls	Cumulative exposure estimates (mg/m^3–years) for individual workers.	Lung			**Odds ratio**	Unadjusted odds ratio; no increasing trend with increasing cumulative exposure; information on smoking habits available for 52% of cases and 75% of controls Assumes a linear trend
				Unexposed	6	1.0	
				<100 mg/m^3–years	5	1.4	
				100–400 mg/m^3–years	6	2.2	
				400–800 mg/m^3–years	3	0.7	
				>800 mg/m^3–years	3	0.9	
				Per 100 mg/m^3–years	23	1.0 (0.9–1.1)	
Wild *et al.* (2002), Luzenac, France (1 site), and Styrian Alps, Austria (4 sites)	Austrian cohort: 542 male talc workers employed >1 year during 1972–95; mortality follow-up, 1972–1995; vital status: 97%;. French cohort: as described under Wild (2000)	Austrian cohort: semi-quantitative, site-specific job-exposure matrix based on personal dust measurements (1988–92) and descriptions of workplaces from management and long-term workers; workers assigned to four categories of exposure: no exposure, ambient (<5 mg/m^3), medium (5–30 mg/m^3) and high (>30 mg/m^3); other exposures coded: quartz, other carcinogens, underground work	All causes			**SMR**	Adjusted for age, calendar year, smoking, exposure to quartz, exposure to other carcinogens, underground work (case–control study); study population overlaps with that of Wild (2000); French SMRs calculated by comparison with regional rates, 1968–95; Austrian SMRs calculated by comparison with regional rates, 1972–1995; Austrian smoking information obtained from unpublished mortality studies on pneumoconiosis, from colleagues, from workers' compensation records; no missing information on smoking habits in Austrian cohort
				French cohort	294	0.9 (0.8–1.0)	
				Austrian cohort	67	0.8 (0.6–1.0)	
			All cancers	French cohort	80	1.0 (0.8–1.3)	
				Austrian cohort	17	0.7 (0.4–1.2)	
			Lung	French cohort	21	1.2 (0.8–1.9)	
				Austrian cohort	7	1.1 (0.4–2.2)	
			Stomach	French cohort	5	1.2 (0.4–2.8)	
				Austrian cohort	1	0.4 (0–2.3)	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wild *et al.* (2002) (contd)	Nested case–control study: lung cancer, non-malignant respiratory disease; three randomly selected controls per case; lung cancer: 23 cases, 67 controls (France); 7 cases, 21 controls (Austria)	Cumulative exposure estimates (mg/m^3–years) assigned to individual workers by occupational physician using work histories abstracted from company records	Lung			**Odds ratio**	Unadjusted odds ratio; no trend observed with increasing cumulative exposure; trend not affected by adjusting for smoking, quartz exposure, underground work or by lagging the exposure estimate
				Unexposed	9	1.0	
				≤100 mg/m^3–years	6	0.9	
				101–400 mg/m^3–years	7	1.1	
				401–800 mg/m^3–years	5	0.6	
				>801 mg/m^3–years	3	0.7	
				Per 100 mg/m^3–years	30	1.0 (0.9–1.1)	Assumes a linear trend
Coggiola *et al.* (2003), Piedmont, Italy	Cohort of 1974 male talc workers employed >1 year in mine or mill during 1946–95; mortality follow-up, 1946–95; loss to follow-up, 9%; analysis based on 1244 miners, 551 millers	Detailed job histories from plant records; workers classified on basis of job held (miner versus miller), duration of exposure (years) and time since first exposure (years)				**SMR**	Adjusted for age, calendar period; study population overlaps with that of Rubino *et al.* (1976, 1979); national death rates used for pre-1970 period; rates for early 1950s used for 1946–49; regional rates used for 1970–95, except for cancers of oral cavity, oesophagus and suicide (regional rates unavailable, national rates used); no information on smoking habits; no variation in lung cancer by duration of exposure
			All causes	Total cohort	880	1.2 (1.1–1.3)	
				Miners	590	1.3 (1.2–1.4)	
				Millers	290	1.1 (1.0–1.2)	
			All cancers	Total cohort	185	1.0 (0.9–1.1)	
				Miners	130	1.1 (1.0–1.3)	
				Millers	55	0.9 (0.6–1.1)	
			Lung cancer	Total cohort	44	0.9 (0.7–1.3)	
				Miners	33	1.1 (0.7–1.5)	
				Millers	11	0.7 (0.3–1.2)	
				Years since first exposure			
				<20	6	1.1 (0.4–2.3)	
				20–30	10	1.0 (0.5–1.8)	
				>30	28	0.9 (0.6–1.3)	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Coggiola *et al.* (contd)						**SMR**	
			Oral cavity	Total cohort	31	5.1 (3.5–7.3)	
				Miners	24	6.2 (3.9–9.1)	
				Millers	7	3.3 (1.3–6.9)	
			Oesophagus	Total cohort	10	2.1 (1.1–3.9)	
				Miners	7	2.3 (0.9–4.8)	
				Millers	3	1.8 (0.4–5.2)	
			Stomach	Total cohort	31	1.2 (0.8–1.6)	
				Miners	20	1.2 (0.7–1.8)	
				Millers	11	1.1 (0.5–2.0)	

CI, confidence interval; mppcf, million parts per cubic foot; SIR, standardized incidence ratio; SMR, standardized mortality ratio

confidence interval (CI), 0.8–1.0) for miners and 0.9 (95% CI, 0.8–1.0) for millers. No relationship was observed with increasing time between first exposure and death or with increasing cumulative exposure. Significant increases in specific cause of death among miners were found for silicosis (62 observed; SMR, 2.0; (95% CI, 1.5–2.6) and for silicosis with superimposed tuberculosis (18 observed; SMR, 2.0; 95% CI, 1.2–3.1). These estimates were found to increase with increasing cumulative exposure. A total of 100 deaths from cancers at all sites combined among miners (SMR, 0.8; 95% CI, 0.6–0.9) and 42 deaths among millers (SMR, 0.9; 95% CI, 0.7–1.2) were below those expected. Nine deaths among miners (SMR, 0.5; 95% CI, 0.2–0.9) and four among millers (SMR, 0.6; 95% CI, 0.2–1.6) were due to lung cancer. No excess risk for lung cancer was found in the highest exposure category among miners (cumulative exposure range, 5666–12750 mppcf–years; five observed; SMR, 1.1; 95% CI, 0.4–2.7) or millers (cumulative exposure range, 425–906 mppcf–years; no observed deaths versus 1.3 expected). No cases of mesothelioma were found. [The Working Group noted that the lack of comparability between the workers and the comparison groups could influence the mortality ratio estimates of this study.]

In a re-analysis of their 1976 study, Rubino *et al.* (1979) estimated relative mortality among talc workers using Italian national death rates for men instead of the control cohort. As national rates were available only for the period 1951–74 (end of the study), rates for 1951 were applied for the follow-up period 1946 through to 1950. The number of workers included in this analysis was 1260 miners and 418 millers. In contrast to the previous analysis, the age-standardized mortality for all causes combined was significantly increased for miners (560 observed; SMR, 1.3; 95% CI, 1.2–1.4) as well as for millers (193 observed; SMR, 1.2; 95% CI, 1.0–1.4). Eight observed cases of lung cancer in miners yielded an SMR of 0.5 (95% CI, 0.2–0.9) and four cases in millers yielded an SMR of 0.7 (95% CI, 0.2–1.7). No trend was observed with increasing cumulative exposure for either group of workers [*p*-value for trend not provided]. Mortality from non-malignant respiratory diseases was significantly increased among miners (109 observed; SMR, 3.3; 95% CI, 2.7–4.0), mainly due to 58 cases of pneumoconiosis and 23 cases of tuberculosis. The number of cases of pneumoconiosis and tuberculosis among millers was three and eight, respectively.

Katsnelson and Mokronosova (1979) conducted a study of mortality among male and female workers [numbers not specified] in a talc mining and processing plant in the former USSR in 1949–75. The talc of the area was reported to contain no tremolite or fibrous materials and levels of quartz ranged from 0.2 to 1.6%. Very high mortality ratios were found for cancer at all sites combined (relative risks, 5.1 for men; 6.4 for women; $P < 0.001$) as well as for lung (relative risks, 4.5 for men; $P < 0.02$; 9.3 for women; $P > 0.05$) and stomach cancer (relative risks, 3.7 for men; $P < 0.02$; 6.3 for women; $P < 0.05$) [observed numbers of deaths not specified]. [The Working Group noted that the deaths observed among exposed workers included current and past workers but that the denominator comprised only currently employed persons.]

Selevan *et al.* (1979) used radiography records from the annual surveys of workers in dusty trades of the Vermont Health Department to identify all white male workers employed in the Vermont talc industry for at least 1 year between 1940 and 1969. The study covered three areas that had a total of five companies (two of which ceased operations in 1952 and 1960). The talc in this region is a mixture of pure talc, magnesite, chlorite and dolomite. Airborne dust samples and bulk materials were free of asbestiform minerals, when examined by both X-ray diffraction and analytical electron microscopy. Levels of respirable crystalline silica were below 0.25% in nearly all ore and product samples, and free silica was only occasionally detectable in air samples. Insufficient information was available to estimate cumulative lifetime exposures, but the authors stated that historical data were sufficient to demonstrate past exposure levels for miners and millers far exceeded the standard for non-fibrous talc of 20 mppcf that was in force at the time of the investigation. Due to the more continuous nature of the milling operation, it was considered probable that exposures to dust for millers were higher than those for miners. In one mine that had closed by the time of the study, 'cobblestones' of highly tremolitic serpentine rock were present but were avoided or discarded as far as possible before milling. Miners were also exposed to radon daughters at mean levels ranging up to 0.12 working levels (WL), with single peaks of 1.0 WL. The study groups comprised 163 talc miners and 225 millers. Vital status of workers was ascertained through to 1975, and death certificates were obtained for 85 of 90 deceased cohort members. For non-malignant respiratory disease and respiratory cancer, mortality rates for white men from Vermont were used for comparison, because they were considered to be more appropriate than national rates. For other causes of death, rates for the USA were used. Some increase was noted for all malignant neoplasms combined (16 observed [SMR, 1.3; 95% CI, 0.7–2.0]) and specifically for respiratory cancer (six observed [SMR, 1.6; 95% CI, 0.6–3.5]). [The Working Group noted that the results for respiratory cancer were not analysed by latency.] The excess mortality from respiratory cancer was statistically significant among the miners (five observed [SMR, 4.3; 95% CI, 1.4–10.1]), but not among the millers (two observed [SMR, 1.0; 95% CI, 0.1–3.7]). A significant excess of mortality from non-malignant respiratory disease was seen in millers (seven observed [SMR, 4.1; 95% CI, 1.6–8.4]), but not in miners (two observed [SMR, 1.6; 95% CI, 0.2–5.9]). Most workers who died from non-malignant respiratory disease had radiographic evidence of pneumoconiosis (rounded opacities).

In two brief communications, Leophonte *et al.* (1983) and Leophonte and Didier (1990) reported on the mortality of workers employed in a talc quarry in Luzenac in the South of France and in the associated talc processing plant. The cohort was composed of those who left employment between 1945 and 1981 and who had worked at the plant for more than 1 year. The talc in this region is a mixture of pure talc, chlorite and dolomite with no asbestos; levels of quartz vary from 0.5 to 3%. Of 470 workers available for study, 256 were alive, 209 had died and five were lost to follow-up. Of 204 workers with a known job history and date of death, 192 had worked exclusively with talc at Luzenac. No significant excess of mortality from cancer in general or specifically from respiratory

and digestive cancers was found. [Observed and expected numbers of cause-specific deaths and associated relative risks were not given.] A significant increase in mortality was found for non-malignant respiratory disease, especially for pneumoconiosis and obstructive lung disease. No cases of mesothelioma were observed. [The Working Group noted the unconventional definition of the cohort and that causes of death were obtained differently for cases (from local doctors, hospitals or families) and controls (from regional or national records).]

Wergeland *et al.* (1990) studied 94 male workers at a talc mine in northern Norway who had been employed in talc-exposed jobs for at least 1 year during 1944–72 and 295 male workers at a talc mill in western Norway who had been employed for at least 2 years during 1935–72. Data on miners were gathered from the company pay rolls, lists of union memberships and the central registry of workers exposed to silica in Norway; data on millers were collected from the company protocol and the local occupational health service. The information included name, date of birth, first and last date of employment and number of periods of employment. According to the authors, Norwegian talc contains only trace quantities of quartz, tremolite and anthophyllite as determined by optical microscopy and by electron microscopic analysis. The talc in the region where the mine was located is composed mainly of pure talc and magnesite. Approximately 90% of the raw material in the mill came from the mine and the rest was imported from India. In addition to talc, dolomite and mica were also processed at the mill. Personal air samples collected in the early 1980s showed that total dust levels varied greatly by job category and workplace (mine, 0.9–97 mg/m^3; mill, 1.4–54 mg/m^3). Peak exposures occurred during drilling in the mine (319 mg/m^3) and in the store house in the mill (109 mg/m^3). X-Ray diffractometry indicated that dust samples from both operations contained less than 1% quartz. The mean value for concentrations of radon daughters in the mine was 3.5 pCi/L [0.04 WL], with a range of 1.5–7.5 pCi/L [0.02–0.08 WL]. The majority of the 389 workers could be classified into one of three categories according to degree of dust exposure, based on measurements and qualified assessments of dust level by experienced co-workers. Information on tobacco smoking habits, gathered during the study in 1981, was available for 63 of the 94 miners and showed that smoking rates among these workers were above the national average. Follow-up for cancer incidence (through data linkage to the national cancer registry) and cause-specific mortality (through linkage to the national mortality files) was begun at the date of entry into the cohort or 1 January 1953, whichever came later, and ended at date of death or 31 December 1987, whichever came first. National rates were used to calculate expected numbers of cancers and deaths. The SMR for all causes for the total cohort was 0.8 (117 observed; 95% CI, 0.6–0.9), which reflected a decrease among both miners (27 observed [SMR, 0.8; 95% CI, 0.5–1.2]) and millers (90 observed [SMR, 0.7; 95% CI; 0.6–0.9]). An excess of deaths from all cancers was observed in miners (nine observed [SMR, 1.3; 95% CI, 0.6–2.5]), but not in either the total cohort (26 observed [SMR, 0.8; 95% CI; 0.5–1.1]) or in millers (17 observed; [SMR, 0.6; 95% CI; 0.4–1.0]). Mortality from non-malignant respiratory diseases was decreased, with one observed death among miners [SMR, 0.4; 95% CI, 0–

2.2] and two observed deaths among millers [SMR, 0.2; 95% CI, 0–0.9]. No deaths from pneumoconiosis were reported. The standardized incidence ratio (SIR) for all types of cancer combined was [1.4 (15 observed; 95% CI, 0.8–2.3)] among the miners and [0.8 (31 observed; 95% CI, 0.5–1.1)] among the millers. Two cases of lung cancer were observed among miners [SIR, 1.6; 95% CI, 0.2–5.7] and four cases among millers [SIR, 0.8; 95% CI, 0.2–2.0]. The non-significant excess risk among the miners was confined to cancer of the stomach (three observed [SIR, 2.5; 95% CI, 0.5–7.4]) and cancer of the prostate (four observed [SIR, 2.0; 95% CI, 0.6–5.2]). In the subgroup of 80 workers who belonged to the highest exposure category, a total of six cases of cancer were observed [SIR, 0.4; 95% CI, 0.2–1.0], none of which were cancer of the lung. There were no observed cases of mesothelioma.

Wild (2000) conducted a retrospective cohort mortality study, within a nested case-control study, at the same talc quarry and milling plant at Luzenac as that used by Leophonte *et al.* (1983) and Leophonte and Didier (1990). The cohort included employees who were active in 1945 or hired in the milling plant during the period 1945–94 and who had been employed continuously for at least 1 year. Employees, who were identified from the company files, comprised a total of 1070 men and 90 women. [The authors did not indicate the extent of overlap of the study population with that investigated by Leophonte *et al.* (1983) and Leophonte and Didier (1990).] Dust levels in the 1960s and 1970s were generally high, ranging from below 5 mg/m^3 to more than 30 mg/m^3. Average dust levels dropped to below 5 mg/m^3 in the 1990s through process changes and installation of engineering controls (e.g. installation of a central vacuum system). Overall mortality of the cohort was evaluated from 1 January 1945 to 31 December 1996. Vital status was obtained from the local population register and national mortality files which also included information on cause of death, in most cases, for individuals who died after 1968. Overall, 32 (2.8%) employees were lost to follow-up. Of 106 individuals who died before 1968, cause of death was ascertained for 78 cases. SMRs were calculated using both regional mortality rates (pre- and post-1968) and national mortality rates (pre-1968). When regional mortality rates for 1968 and later were used, the SMR for all causes of death combined was 0.9 (294 observed; 95% CI, 0.8–1.0) for men and 0.8 (11 observed; 95% CI, 0.4–1.4) for women. Eighty men died from cancer at any site (SMR, 1.0; 95% CI, 0.8–1.3) and 21 died from lung cancer specifically (SMR, 1.2; 95% CI, 0.8–1.9). Mortality from lung cancer was non-significantly increased in subgroups of employees who were under 60 years of age (seven observed; SMR, 2.0 [95% CI, 0.8–4.0]), had a latency period of less than 20 years (five observed; SMR, 2.4 [95% CI, 0.8–5.6]) or had a duration of employment of less than 10 years (eight observed; SMR, 2.1 [95% CI, 0.9–4.1]). A slightly increased risk was seen for stomach cancer (five observed; SMR, 1.2; 95% CI, 0.4–2.8). Twenty-six men died from non-malignant respiratory diseases (SMR, 1.1; 95% CI, 0.7–1.6), three of which were pneumoconiosis (SMR, 5.6; 95% CI, 1.1–16.2). When pre-1968 national reference rates were applied, the overall SMR for men was 0.8 (101 observed; 95% CI, 0.6–1.0) and the excess mortality from lung cancer and non-malignant respiratory diseases disappeared. Of

the 101 deaths observed during this period, one was caused by lung cancer (SMR, 0.3 [95% CI, 0.7–1.5]) and five were caused by non-malignant respiratory diseases (SMR, 0.7 [95% CI, 0.2–1.6]). A nested case–control study was performed to investigate further the risks for lung cancer, stomach cancer and non-malignant respiratory diseases in the men of the cohort. For the lung cancer case–control study, 67 controls were individually matched to the 22 cases by age and sex (approximately three controls per case). Information on job history at the plant and tobacco consumption was collected through interviews of subjects who were alive and/or from experienced co-workers. A semiquantitative site-specific job–exposure matrix for talc dust was established using dust levels measured from 1986 onwards and estimates of levels before that year. Information on job history was then converted into estimates of cumulative exposure of the individual employees (expressed as mg/m^3–years). Multiple logistic regression analysis with adjustment for tobacco smoking habits and exposure to quartz estimated the odds ratio for lung cancer to be 0.7 (three cases and 15 controls) and 0.9 (three cases and 10 controls) for employees with a cumulative exposure to talc dust of 400–800 mg/m^3–years and more than 800 mg/m^3–years, respectively, when compared with unexposed employees (six cases and 20 controls). [The Working Group noted that information on smoking habits was available for only 52% of cases and 75% of controls, and that no specific information was given on the proportion of subjects alive among cases and controls at the date of interview.]

Wild *et al.* (2002) conducted a combined analysis of previously published cohort mortality studies among 1070 male employees at a talc quarry and milling plant in the south of France (Site A) (Wild, 2000) and 542 male employees at three talc mines and their respective mills in Austria (Sites B, C and D). The Austrian cohort comprised workers who had been employed for at least 1 year between 1 January 1972 and 31 December 1995. Complete work histories for the Austrian workers were abstracted from company registries and from the regional social insurance. Information on tobacco smoking habits was obtained from earlier unpublished studies of mortality and pneumoconiosis, from colleagues and from records of the compensation claim insurance. Talc from two of the three Austrian plants (Sites B and C) had a content of quartz that was less than 4%, while that of the third plant (Site D) had higher but unspecified levels. Vital status of workers was verified through to 1995, and cause of death for those who had died was obtained from national mortality files. Local mortality rates yielded an overall SMR for the Austrian cohort of 0.8 (67 observed; 95% CI, 0.6–1.0;). A total of 17 deaths were due to cancer at any site (SMR, 0.7; 95% CI, 0.4–1.2), seven of which were from cancer of the lung (SMR, 1.1; 95% CI, 0.4–2.2). One death from stomach cancer (SMR, 0.4; 95% CI, 0–2.3) and no deaths from mesothelioma (0.1 expected) occurred. On the basis of 23 lung cancer deaths observed in the French cohort in 1968–96 and seven in the Austrian cohort in 1972–95, a nested case–control study was conducted. A total of 88 control subjects were selected from the two cohorts, individually matched to cases on age, calendar period and company. All job tasks at the companies were categorized according to measured and estimated levels of talc dust into one of four

exposure groups (no exposure, < 5 mg/m^3, 5–30 mg/m^3 and > 30 mg/m^3). Job histories of cases and controls were converted into cumulative exposure to talc dust by summing the products of duration and level of exposure for each of the tasks held by the subject (mg/m^3–years). Subjects were also categorized according to tobacco smoking habits, exposure to quartz or a history of underground work on a yes/no basis. Information on smoking habits was available for approximately 50% of the cases and 75% of the controls in the French cohort and for 100% of the Austrian cohort. When the no-exposure category was used as the standard (nine cases, 23 controls), the unadjusted odds ratios for lung cancer were as follows: 0.9 (exposure category, 1–100 mg/m^3–years; six cases, 18 controls); 1.1 (exposure category, 101–400 mg/m^3–years; seven cases, 15 controls), 0.6 (exposure category, 401–800 mg/m^3–years; five cases, 21 controls) and 0.7 (exposure category, > 801 mg/m^3–years; three cases, 10 controls). Assuming a linear trend, the odds ratio was 1.0 (95% CI, 0.9–1.1) per unit of 100 mg/m^3–years. Adjustment for tobacco smoking, exposure to quartz or underground work or any two of these variables did not change the results.

Coggiola *et al.* (2003) updated the cohort of Rubino *et al.* (1976, 1979) to include 1974 men who had worked for at least 1 year in the mine and/or in the factory during the period 1946–95. The mortality analysis included 1795 subjects (90.9% of the total cohort; 1244 miners and 551 millers), after excluding 179 workers who were lost to follow-up. No data on smoking habits were available. Follow-up began on 1 January 1946 or the date of first employment and ended at the date of death or 31 December 1995, during which time a total of 880 deaths occurred. The expected number of deaths was calculated from national rates for 1950–69 and regional mortality rates for 1970 onwards (with the exception of cancers of the oral cavity and oesophagus for which regional rates were unavailable; national rates were therefore used). Rates for the early 1950s were applied for the period 1946–49. Total mortality among workers was higher than expected (880 observed; SMR, 1.2; 95% CI, 1.1–1.3), mainly due to excess mortality from non-malignant respiratory tract diseases among the subgroup of miners (105 observed; SMR, 3.1; 95% CI, 2.5–3.7). Of the 105 deaths in this category, 58 were from silicosis. In the combined cohort of workers, there was no excess mortality for all cancers (185 observed; SMR, 1.0; 95% CI, 0.9–1.1) or for lung cancer, in particular (44 observed; SMR, 0.9; 95% CI, 0.7–1.3). No deaths from pleural or peritoneal mesothelioma were found. A significantly elevated risk was seen for cancers of the oral cavity (31 observed; SMR, 5.1; 95% CI, 3.5–7.3) and the oesophagus (10 observed; SMR, 2.1; 95% CI, 1.1–3.9). When the analysis was stratified by job, the SMR for lung cancer was 1.1 (33 observed; 95% CI, 0.7–1.5) among miners and 0.7 (11 observed; 95% CI, 0.3–1.2) among millers. The slight excess found among miners seemed to be due to a slightly elevated risk in workers with less than 20 years since first exposure (latency) (six observed; SMR, 1.1; 95% CI, 0.4–2.3) compared to that of workers with 20–30 years (10 observed; SMR, 1.0; 95% CI, 0.5–1.8) and more than 30 years (28 observed; SMR, 0.9; 95% CI, 0.6–1.3) since first exposure. There was no variation in lung cancer mortality by duration of exposure. Cancer of the oral cavity caused the death of 24 miners (SMR, 6.2; 95% CI, 3.9–9.1) and

seven millers (SMR, 3.3; 95% CI, 1.3–6.9) and oesophageal caused the death of seven miners (SMR, 2.3; 95% CI, 0.9–4.8) and three millers (SMR, 1.8; 95% CI, 0.4–5.2). Excess mortality was seen in miners for non-malignant respiratory tract diseases (105 observed; SMR, 3.1; 95% CI, 2.5–3.7), non-malignant digestive tract diseases (50 observed; SMR, 1.4; 95% CI, 1.0–1.8) and liver cirrhosis (37 observed; SMR, 1.8; 95% CI, 1.3–2.5). An increased risk for liver cirrhosis was also observed in millers (18 observed; SMR, 1.7; 95% CI, 1.0–2.7).

Meta-analysis of risk for lung cancer

Wild (2006) performed a meta-analysis of lung cancer mortality among miners and millers from industries that produced non-asbestiform talc in Vermont, USA (Selevan *et al.*, 1979), Norway (Wergeland *et al.*, 1990), Italy (Coggiola *et al.*, 2003), France (Wild, 2000) and Austria (Wild *et al.*, 2002). The purpose of the analysis was to compute risk estimates separately for talc miners, who usually have some co-exposure to silica and/or radon daughters, and talc millers, who normally have no such co-exposure. Previously unpublished risk estimates for the subgroup of millers in the French and Austrian cohorts were used and additional information on smoking habits was obtained for Italian, French and Austrian workers. Data indicated that the prevalence of smoking was higher than that in the reference populations [figures not specified]. In the estimation of the overall risk for millers, data from all five countries were used, while only data from the USA, Norway and Italy were included in that for miners. Based on SMRs for lung cancer of 1.0 (USA; two cases; 95% CI, 0.1–3.7), 0.7 (Italy; 11 cases; 95% CI, 0.3–1.2), 1.2 (France; 21 cases; 95% CI, 0.8–1.9), 0.7 (Austria, Site B; three cases; 95% CI, 0.1–2.0) and 1.1 (Austria, Site C; one case; 95% CI, 0–6.2) and an SIR of 0.8 (Norway; four cases; 95% CI, 0.2–2.0) for talc millers, a summary SMR of 0.92 (42 cases; 95% CI, 0.7–1.3) was obtained. No heterogeneity between studies was detected. Similarly, based on mortality ratios for lung cancer of 4.4 (USA; five cases; 95% CI, 1.4–10.2) and 1.1 (Italy; 33 cases; 95% CI, 0.7–1.5) and an incidence ratio of 1.6 (Norway; two cases; 95% CI, 0.2–5.7) for talc miners, a summary SMR of 1.2 (40 cases; 95% CI, 0.9–1.6) was found. Due to a significant heterogeneity of the latter data set, a random effect estimate of the overall SMR was also calculated (40 cases; SMR, 1.9; 95% CI, 0.7–5.1).

2.1.2 *User industries* (Table 2.2)

Information on risk for cancer among workers exposed to talc is available from studies that were conducted in user industries. However, they are less informative than those conducted in talc miners and millers because the potential contamination of talc was not addressed. In addition, these studies provided no details about the type of talc used.

(a) Manufacture of ceramic plumbing fixtures

Thomas and Stewart (1987) conducted a cohort mortality study of 2055 white men employed for at least 1 year between 1939 and 1966 at three plants of a single company in

Table 2.2. Cohort studies of mortality from and incidence of cancer in workers occupationally exposed to non-asbestiform talc in user industries

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Manufacture of ceramic plumbing fixtures							
						SMR	
Thomas & Stewart (1987), USA, 5 plants in 1 company	2055 white men employed >1 yearm 1939–66; mortality follow-up through to 1 Jan. 1981; vital status, 96%	Exposure to silica and talc assessed qualitatively by job title–department by industrial hygienist	All causes	Total cohort	587	0.9 [0.8–1.0]	Crystalline silica was the major exposure; also exposure to non-fibrous and fibrous talc
			Lung cancer	Total cohort	52	1.4 [1.1–1.9]	
				High silica	44	1.8 [1.3–2.4]	
				High silica+non-fibrous talc	21	2.5 [1.6–3.9]	
				High silica+non-fibrous talc+fibrous talc	5	1.7 [0.6–4.0]	
				High silica+no talc	18	1.4 [0.8–2.2]	
Manufacture of pulp and paper							
						SIR	
Langseth & Andersen (1999), Norway, 10 paper mills	4247 women employed >1 year, 1920–93; follow-up of cancer incidence, 1953–93		All cancers	Total cohort	380	1.2 (1.1–1.3)	Comparison with 5-year age-specific rates in Norwegian women; cancer incidence from National Cancer Registry
			Ovarian cancer		37	1.5 (1.1–1.2)	
			Exposure ≥3 years		31	1.6 (1.1–2.3)	
			Age 25–35 years		6	8.0 (2.9–17.4)	
			Ovarian cancer	Paper mill workers	18	2.1 (1.3–3.4)	

Table 2.2 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Langseth & Kjaerheim (2004), Norway, 10 paper mills	Nested case–control study in cohort of Langseth & Andersen (1999); 46 cases, 179 matched controls; 100% histologically confirmed	Exposure to asbestos, talc and total dust from work histories, questionnaires by industrial hygienists/ senior employees and international database; personal use of talc: 76% of cases, 57% of controls; personal interviews	Ovarian cancer	Total dust Ever talc Ever asbestos Asbestos according to interview		**Odds ratio** 0.8 (0.4–1.7) 1.1 (0.6–2.2) 2.0 (0.7–5.7) 2.2 (0.5–9.1)	Parity, breastfeeding, tobacco smoking habits, family history of breast or ovarian cancer; conditional logistic regression; odds ratios unchanged after adjustment for confounders
Rubber manufacturing industries							
Blum *et al.* (1979), USA, 2 rubber companies	Nested case–control study; 100 cases, 4 controls per case; matched on age, race, sex, company; 1964–73	Exposure to polycyclic hydrocarbons, nitrosamines, carbon black, talc (high, moderate, low, none) from job histories	Stomach cancer	*Company A* High+moderate talc High talc	 27 13	 2.4 (1.4–4.1)* 1.3 (0.9–2.5)*	No information on composition or purity of talc; no increase in risk in Company B *90% CI

Table 2.2 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Straif *et al.* (1999), Germany, 5 rubber production plants	8933 male blue-collar workers hired after 1 Jan. 1950 and alive 1 Jan. 1981; follow-up, 1 Jan. 1981 to end of 1991; cause of death known for 97% of 1521 deceased	Work histories recontructed from cost centre codes	Lung cancer Stomach cancer		154 44	**SMR** 1.2 (1.0–1.4) 1.2 (0.8–1.6)	SMRs calculated from national death rates
Straif *et al.* (2000), Germany, 5 rubber production plants	Same as that of Straif *et al.* (1999)	Same as Straif *et al.* (1999) plus semi-quantitative cumulative exposure (low, medium, high) to asbestos, talc, nitrosamines, carbon black for 95% of cohort	Lung cancer Stomach cancer Laryngeal cancer	High talc Medium talc High talc Medium talc High talc Medium talc	21 41 11 12 3 2	1.9 (1.1–3.1) 1.1 (0.8–1.6) 4.3 (2.1–9.0) 1.2 (0.6–2.4) 5.4 (1.1–27.0) 2.8 (0.5–16.7)	Unadjusted; reference: low exposure to talc

CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio

the USA that manufactured ceramic plumbing fixtures. Crystalline silica was said to be the major occupational exposure of these workers, but, in some parts of the plant, exposure to fibrous [tremolitic] and non-fibrous [tremolite-free] talc had also occurred. Vital status was ascertained for 96% of the cohort through to 1 January 1981 and observed numbers of deaths were compared with numbers expected from cause-specific mortality rates for white men in the USA. For each job title–department combination, exposure to silica and talc were qualitatively assessed by an experienced industrial hygienist. Silica exposure was categorized as none, low or high; high exposure to silica was further categorized on the basis of no exposure to talc, exposure to fibrous talc and exposure to non-fibrous talc. The SMR for all causes combined was 0.9 (578 observed [95% CI, 0.8–1.0]) and that for lung cancer was 1.4 (52 observed [95% CI, 1.1–1.9]). The excess mortality from lung cancer was seen exclusively among workers who had been exposed to high levels of silica dust (44 observed; SMR, 1.8 [95% CI, 1.3–2.4]) and, to a greater extent, in the subgroup with additional exposure to non-fibrous talc (21 observed; SMR, 2.5 [95% CI, 1.6–3.9]) than in subgroups with additional exposure to fibrous talc (five observed; SMR, 1.7 [95% CI, 0.6–4.0]) or no exposure to talc (18 observed; SMR, 1.4 [95% CI, 0.8–2.2]). [The Working Group noted that all jobs that involved exposure to talc also involved high exposure to respirable silica.]

(b) Manufacture of pulp and paper

Langseth and Andersen (1999) examined cancer incidence among a cohort of 4247 women who had been employed for at least 1 year between 1920 and 1993 in the Norwegian pulp and paper industry. The women had worked mainly in paper sorting and packing departments in 10 paper mills or in administration (85% of the cohort). Production was judged to involve occupational exposures that included paper dusts, microbes, formaldehyde, talc and asbestos (the latter was used as insulation material in boilers and in the breaks of various rolling machines), but no measurement data were available. Women were followed for cancer incidence between 1953 and 1993 and SIRs were calculated by comparing the observed incidence to the 5-year age-specific incidence rates for the female population of Norway. Information on cancer incidence was obtained by linkage with the National Cancer Registry and information on dates of death and emigration was obtained from the Central Bureau of Statistics of Norway. Records of women who died between 1953 and 1960 were identified manually. Between 1953 and 1993, 535 women in the cohort had died, 65 women had emigrated and 380 new cases of cancer had been diagnosed. The SIR for all cancers was 1.2 (380 observed; 95% CI, 1.1–1.3). An excess of ovarian cancer diagnoses was observed (37 observed; SIR, 1.5; 95% CI, 1.1–2.1). In the analyses, workers were also stratified by exposure into the following categories: short-term (< 3 years) versus long-term (≥ 3 years); period of first exposure (1920–39, 1940–59, 1960–74, 1975–93); and time since first exposure (3–14 years, 15–29 years, ≥ 30 years). The excess risk was predominantly seen among women who had been employed in the industry for 3 years or more (31 observed; SIR, 1.6; 95% CI, 1.1–2.3). The excess risk for ovarian cancer was also highest for women under the age of

55 years at diagnosis, with an SIR of 8.0 (six observed; 95% CI, 2.9–17.4) for women aged 25–35 years at diagnosis. Among women who worked in the paper mills, the SIR for ovarian cancer was 2.1 (18 observed; 95% CI, 1.3–3.4). In the discussion, the authors noted that talc is added as a filler in paper mills and may contribute to the excess risk for ovarian cancer observed.

On the basis of an extended follow-up of cohort members for cancer incidence to the end of 1999, Langseth and Kjaerheim (2004) conducted a nested case–control study that included 46 employees who had ovarian cancer and 179 controls individually matched to cases by incidence density sampling. An experienced oncologist reviewed the pathology for all cases. Work histories were obtained from personnel records at each mill. Exposure to asbestos, talc and total dust was assessed on the basis of the work histories, questionnaires on production processes completed by industrial hygienists and senior employees, as well as semiquantitative exposure assessments for the 10 mills extracted from an international database of exposure in the pulp and paper industry. Information on possible confounders (including use of talc on sanitary napkins, underwear or diapers) was obtained for 76% of cases and 57% of controls through a personal interview with the study subject or next of kin. Odds ratios for ovarian cancer were derived by conditional logistic regression. Ever exposure to asbestos was associated with a non-significantly increased odds ratio for ovarian cancer of 2.0 (95% CI, 0.7–5.7), while ever exposure to talc (odds ratio, 1.1; 95% CI, 0.6–2.2) or to total dust (odds ratio, 0.8; 95% CI, 0.4–1.7) was associated with risks that were close to unity. Among women who were interviewed, the odds ratio for exposure to asbestos was 2.2 (95% CI, 0.5–9.1). This estimate was unchanged after adjustment for multiple potential confounders, including parity, breastfeeding, tobacco smoking habits and family history of breast or ovarian cancer. The odds ratios for occupational exposure to talc and total dust were similarly unchanged after adjustment for confounding.

(c) Rubber manufacturing industries

Following the finding of an excess risk for stomach cancer in a cohort of rubber workers in the USA, Blum *et al.* (1979) carried out a nested case–control study of stomach cancer. Cases were defined as deaths from stomach cancer in two of the rubber companies from 1 January 1964 to 31 December 1973 (100 deaths in total). Four controls were matched to each case on age, race, sex and company. Using the recorded job history of each worker, the investigators and a group of environmental scientists assessed the potential for exposure (high, moderate, low or none) in each job to the following substances: polycyclic hydrocarbons, nitrosamines, carbon black and detackifiers (anti-sticking agents which were mainly talc). No information was available on the purity or composition of the talc (i.e. whether it contained asbestiform materials or other fibrous or non-fibrous carcinogens). While no clear elevation of odds ratio was reported in Company B, a significantly increased relative risk of 2.4 (27 observed; 90% CI, 1.4–4.1) was found in Company A when workers with moderate and high exposure to talc were

pooled into one group. High exposure in the latter company was associated with a modest increase in relative risk of 1.3 (13 observed; 90% CI, 0.7–2.5).

Based on the employment files of five rubber production plants in Germany, Straif *et al.* (1999) conducted a mortality cohort study of 8933 male blue-collar workers who were hired after 1 January 1950 and who were alive on 1 January 1981. Follow-up was started on the date of completion of 1 year of employment or 1 January 1981, whichever came last, and ended on at death, at 85 years of age, at the date of loss to follow-up or 31 December 1991, whichever came first. Cause of death was obtained for 97% of 1521 deceased workers. Work histories were reconstructed from cost centre codes and were classified into six work areas. SMRs were calculated from national death rates and were estimated at 1.2 (154 observed; 95% CI, 1.0–1.4) for lung cancer and 1.2 (44 observed; 95% CI, 0.8–1.6) for stomach cancer. In a subsequent analysis (Straif *et al.*, 2000), information on work history was combined with semiquantitative levels of exposure to asbestos, talc, nitrosamines and carbon black that were estimated by industrial hygienists to yield overall estimates of cumulative exposure (low, medium, high) for approximately 95% of the cohort. Talc is widely used in rubber production and, according to the authors, asbestos was used in all five plants at least until the early 1980s. In risk analyses that were unadjusted for exposure to asbestos or other potential workplace confounders, high and medium occupational exposure to talc were associated with relative risks for lung cancer of 1.9 (21 observed; 95% CI, 1.1–3.1) and 1.1 (41 observed; 95% CI, 0.8–1.6), respectively, when workers with low exposure were used as the reference group. Equivalent risk estimates were 4.3 (11 observed; 95% CI, 2.1–9.0) and 1.2 (12 observed; 95% CI, 0.6–2.4) for stomach cancer and 5.4 (three observed; 95% CI, 1.1–27.0) and 2.8 (two observed; 95% CI, 0.5–16.7) for laryngeal cancer. Separate risk analyses with adjustment for potential confounders were not performed. [The Working Group noted that risk analyses that adjusted for estimates of exposure to asbestos were not presented.]

2.1.3 *Community-based studies*

Chen *et al.* (1992) conducted a case–control study in Beijing, China, of several risk factors for ovarian cancer that included occupational exposure to talc. A total of 220 cases of newly diagnosed epithelial ovarian cancer were identified between 1984 and 1986 through the Beijing Cancer Registry. Of these, 67 [30.5%] were excluded due to death, 37 [16.8%] due to unavailability of current contact information and four [1.8%] due to patient refusal. The analysis was carried out on 112 cases and 224 community controls, with two age-matched controls per case. Potential controls were excluded if they had a history of serious illness, although the percentage of those excluded for this reason was not specified. In addition, 15 of the 224 eligible controls initially selected [6.7%] refused to participate in the study and were therefore replaced by other eligible controls. No information was provided on the age range of the cases and controls, although the mean age at the time of interview was similar for cases (48.5 years) and controls (49.0 years).

All cases were confirmed by laparotomy and pathological review. Data were collected in-person by trained interviewers. Odds ratios were estimated using conditional logistic regression adjusted for education and parity. Occupational exposure to talc was associated with an odds ratio for ovarian cancer of 0.9 (95% CI, 0.3–2.9). [The Working Group noted the incomplete ascertainment of cases of ovarian cancer due to the nature of the cancer-reporting system in China, the large number of cases who were excluded due to death and the exclusion of controls who had a history of serious health problems, which may have resulted in selection bias.]

Hartge and Stewart (1994) analysed the occupational histories of 296 women aged 20–79 years who were diagnosed with ovarian cancer between 1978 and 1981 in the Washington DC area of the USA and 343 hospital-based controls matched to cases on age and race. Pathology was confirmed for all cases. Trained interviewers used a standardized questionnaire to obtain information from each participant on their lifetime job history and occupational exposure to talc. An industrial hygienist blinded to the case status of each participant evaluated each industry and occupation for potential exposure to talc, ionizing radiation, polycyclic aromatic hydrocarbons and solvents, using a scale of 0 (definitely not exposed) to 4 (definitely exposed). Women were considered to be exposed if they had an exposure rating of 2–4 (possibly, probably or definitely exposed). Logistic regression adjusted for race, age, parity, gynaecological surgery and duration of employment in jobs with the exposure of interest was used for the analyses. Controlling for additional known and potential risk factors for ovarian cancer, including parity, oral contraceptive use and cigarette smoking, did not change these estimates. Women who were classified as having been occupationally exposed to talc had odds ratios below the null, although the confidence limits were wide due to the small number of exposed women (12 cases, 31 controls). For women with 10 or more years of employment in an occupation with possible, probable or definite exposure to talc, the odds ratio was 0.5 (five exposed cases; 95% CI, 0.2–1.5). The risk for ovarian cancer was not significantly elevated for any exposure or duration of employment assessed. [Limitations of this analysis include the small number of women occupationally exposed to talc.]

'Industrial talc' was one of the substances evaluated by the exposure assessment team in the community-based case–control study carried out in Montréal, Canada (Siemiatycki, 1991) and described in detail in the monograph on carbon black. About 5% of the 4263 study subjects was considered to be exposed to industrial talc, mostly in the following occupations: painters, motor vehicle mechanics and farmers. Exposure to talc was analysed in relation to 11 different types of cancer, at two levels of exposure (any or substantial). No statistically significant increases in risk were observed. The odds ratios for lung cancer were 0.9 (35 exposed cases; 90% CI, 0.6–1.4) for 'any exposure' and 0.9 (nine exposed cases; 90% CI, 0.5–1.9) for 'substantial exposure'. Prostate cancer was the only site with a borderline significant increased risk, with an odds ratio of 1.4 (29 exposed cases; 90% CI, 1.0–2.1) for 'any exposure' and 1.1 (seven exposed cases; 90% CI, 0.5–2.3) for 'substantial exposure'. [The main limitation of the study was the reliance on expert opinions of exposure rather than measurements for exposure

assessment. Also, exposure levels tend to be lower in such community-based studies than in the workplaces that are selected for cohort studies. The main advantages were the availability of histologically confirmed incident cases and detailed information on tobacco smoking habits and other characteristics of the subjects.]

2.2 Cosmetic use of talc

This evaluation was limited to ovarian cancer because the Working Group was unaware of studies of other cancers associated with the cosmetic use of talc.

The content of body powders used by women varies by product and has changed over time, although data that document this are limited. Before the mid-1970s, body powders may have contained varying but usually small quantities of amphiboles. After that time, amphibole was voluntarily reduced to less than detectable levels, at least in western Europe and the USA. Other non-talc minerals that include chlorite, quartz, carbonates and pyrophyllite may also be found in body powders in varying and occasionally not insignificant quantities in the past and currently. Other added ingredients, which depend on the product, could include cornstarch and perfumes.

2.2.1 *Cohort studies*

Gertig *et al.* (2000) carried out the only prospective cohort analysis that reported an association between perineal use of talcum, baby or deodorant powder and the risk for ovarian cancer. This analysis was conducted among participants in the Nurses' Health Study, a cohort of 121 700 female registered nurses who had been followed since 1976. All participants were between the ages of 30 and 55 years and lived in one of 11 states of the USA at study enrolment. Questionnaires were mailed to participants every 2 years beginning in 1976 to obtain information on the medical history of each woman and potential risk factors for cancer, heart disease and other conditions. The 1982 questionnaire requested information on history and frequency of application of powder to the perineal area (none, daily, one to six times a week, less than once a week) and history of application of powder to sanitary napkins (no/yes). 'Ever talc use' was classified as ever use on either the perineal area or on sanitary napkins. The study population included 78 630 women who responded to the questions on powder use in 1982 and who were not excluded from the analysis for another reason (cancer other than non-melanoma skin cancer before 1982, bilateral oophorectomy, surgery with unknown number of ovaries removed or radiation therapy) and entailed 984 212 person–years of follow-up. Between 1982 and June 1996, 307 incident cases of epithelial ovarian cancer were identified by self-reporting in a biennial questionnaire, by deaths that were reported by relatives or postal authorities or through the National Death Index. Physicians blinded with respect to exposure status reviewed pathology reports to confirm each case and to determine the histological subtype for each tumour as reported by the woman's pathologist. Pooled logistic regression was used to model the incidence rate ratio of ovarian cancer for the

exposed versus unexposed participants. The reported results were adjusted for age in years, parity (defined as the number of pregnancies lasting 6 months or more), duration of oral contraceptive use, body mass index, history of tubal ligation, tobacco smoking status and postmenopausal use of hormones. Additional covariates considered as potential confounders included age at menarche, duration of breastfeeding and age at menopause. Family history of ovarian cancer was not considered to be a confounder, since information on this covariate was not collected until 1992. In 1982, 40.4% of the cohort reported a history of perineal talc use ($n = 31\ 789$) and 14.5% reported a history of daily use ($n = 11\ 411$). Overall, no association between 'ever use' of talcum powder and total risk for epithelial ovarian cancer (relative risk, 1.1; 95% CI, 0.9–1.4) and no trend of increased risk for ovarian cancer with increasing frequency of talc use were observed. However, a modest increase in risk for serous invasive cancers was associated with any history of talc use (relative risk, 1.4; 95% CI, 1.0–1.9) and a borderline significant trend was found with increasing frequency of use (p for trend = 0.05). Among women without a history of tubal ligation, no association was observed between history of talc use and total risk for epithelial ovarian cancer (relative risk, 1.0; 95% CI, 0.7–1.3). Similarly, history of tubal ligation did not modify the association between the use of talc and risk for serous invasive cancers. [Limitations of this analysis include the availability of exposure information at a single time-point only, the relatively short follow-up period after exposure assessment and the lack of information on age at first use of talc, duration of use of talc, current use of talc in 1982 and use of talc before tubal ligation or pregnancy, all of which are potentially important parameters based on previous studies.]

2.2.2 *Case–control studies* (Table 2.3)

Cramer *et al.* (1982) reported the first epidemiological study of genital talc use and the risk for ovarian cancer. The analysis included 215 cases of epithelial ovarian cancer and 215 population-based controls matched to cases by age (within 2 years), race and residence. All cases were Caucasian, English-speaking residents of Massachusetts, USA, aged 18–80 years, who had been diagnosed with epithelial ovarian cancer between November 1978 and September 1981. Cases were identified through pathology logs or tumour boards of 12 participating Boston hospitals. Among 297 eligible cases identified during the time period of interest, 41 were excluded from the study due to: physician refusal (13), patient refusal (14) or death/change of address (14). An additional 41 cases were excluded because they had a non-ovarian primary (18) or a non-epithelial ovarian tumour based on a review of pathology specimens by the authors. Controls were identified though annual listings of the names, addresses and ages of all Massachusetts residents. Among 475 women identified as potential controls, 11.8% (56) could not be reached, 6.1% (29) were ineligible due to previous bilateral oophorectomy, 4.2% (20) were the wrong age, not Caucasian or did not speak English and 32.6% (155) refused to participate. All cases and controls were interviewed in person to obtain information on their medical history, menstrual and reproductive histories, as well as potential for exposure

Table 2.3. Case–control studies of epithelial ovarian cancer (invasive or borderline) and cosmetic use of talc

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Cramer *et al.* (1982) Boston, MA, USA, 1978–81	215 Caucasian, English-speaking women, aged 18–80 years; identified through pathology logs or tumour boards of 12 Boston hospitals; histological confirmation of diagnosis; 215 population-based controls identified through annual listings of names, ages and addresses of all Massachusetts residents; matched by age (±2 years), race, residence	In-person interviews; information collected on medical history, menstrual and reproductive history, potential or definite exposure to talc	'Any' perineal exposure to talc As dusting powder on perineum and sanitary napkins	92 32	1.6 (1.0–2.5) 3.3 (1.7–6.4)	Parity, menopausal status, religion, marital status, educational level, weight, age at menarche, exact parity, oral contraceptive use, postmenopausal use of hormones, tobacco smoking	Distribution of tumour histologies similar for exposed and unexposed cases; potential for talc exposure by way of contraceptives, pelvic surgery or perineal hygiene considered; no information on duration or frequency of talc use; low participation rates among controls (56% of cases matched with no refusals; 27% matched after 1 refusal; 17% matched after 2 or more refusals)
Hartge *et al.* (1983) Washington DC, USA, 1974–77	135 incident cases treated at participating hospitals; 171 population-based controls; frequency-matched by age, race, hospital	Interviews to collect information on reproductive and sexual history, medical history, drug use and other exposures, exposure to talc categorized as 'any' or 'genital' (includes use on genitals, on sanitary napkins or on underwear)	'Any' use of talc 'Genital' exposure to talc	67 7	0.7 (0.4–1.1) 2.5 (0.7–10.0)	Age, race, pregnancy	Questions on talc added after study began; no information on duration or frequency of exposure; no controlling for other potential confounders; potential for selection bias

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Whittemore *et al.* (1988), San Francisco, CA, USA 1983–85	188 incident cases diagnosed at 8 hospitals, aged 18–74 years; histological verification of diagnosis; 539 controls selected from women hospitalized for non-cancerous conditions (*n*=280) or from the population using random digit-dialling (*n*=259); matched by age (±5 years), race, hospital/date of admission (hospital controls) or telephone area code/prefix (population controls)	Structured in-person interviews; information collected on medical history, menstrual and reproductive history, family history, environmental exposures (talc, coffee, alcohol, tobacco); talc exposure categorized by type of application, duration of use prior to tubal ligation or hysterectomy, frequency of use	*Type of application*				No trend of increasing risk with increasing duration of exposure, as measured in years of talcum powder use on the perineum prior to tubal ligation or hysterectomy; non-statistically significant trend of increasing risk with increasing frequency of exposure, as measured in number of applications of talc to the perineum per month
			Perineum only	22	1.5 (0.8–2.6)	Parity, oral contraceptive use	
			Sanitary pads only	5	0.6 (0.2–1.8)		
			Diaphragm only	9	1.5 (0.6–3.6)		
			Any two	67	1.4 (0.9–2.0)		
			All three	1	0.4 (0.0–2.9)		
			Duration of use (years)			Parity	
			None	103	1.0		
			1–9	34	1.6 (1.0–2.6)		
			≥10	50	1.1 (0.7–1.7)		
			Frequency of use			Parity	
			Never	97	1.0		
			1–20 times/month	41	1.3 (0.8–2.0)		
			≥20 times/month	44	1.5 (0.9–2.2)		
			30 times/month	–	1.3 (0.9–1.9)		
			p for trend		0.19		

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Booth *et al.* (1989), London and Oxford, United Kingdom, 1978–83	235 incident cases from 15 hospitals, aged 65 years or under at diagnosis; diagnosed within 2 years of interview; histological confirmation of diagnosis; 451 hospital-based controls selected from same 15 hospitals; same age distribution as the cases	Interviewer- administered standard questionnaire; information obtained on reproductive and menstrual history, on exposure to exogenous estrogens, cigarettes, talc; talc exposure categorized by frequency of use on perineum and whether it was used to store a diaphragm	*Frequency of use* Never Rarely Monthly Weekly Daily *p* for trend	 76 6 7 57 71	 1.0 0.9 (0.3–2.4) 0.7 (0.3–1.8) 2.0 (1.3–3.4) 1.3 (0.8–1.9) 0.05	Age, socioeconomic status	Participation rates not provided; questions on talc use added 3 months after start of study; data on talc exposure missing for 18 cases and 17 controls
Harlow & Weiss (1989), western Washington State, USA, 1980–85	116 Caucasian women from 3 urban counties captured in Seattle-Puget Sound Cancer Surveillance System, aged 20–79 years; independent pathological review: 73% of total; histological agreement: 94% of reviewed cases; 158 white population-based controls selected by random-digit dialling; matched by age, county of residence	In-person interviews; information obtained on reproductive, sexual and medical histories, as well as perineal exposure to talc; talc exposure categorized as 'any' perineal use, by method of use, and by type of powder used.	'Any' perineal use *Type of powder used* Cornstarch only Baby powder only Baby powder, combined Talc, unspecified Deodorizing powder only Deodorizing, combined	49 4 18 22 13 10 14	1.1 (0.7–2.1) 0.8 (0.2–3.8) 0.8 (0.4–1.9) 0.9 (0.5–2.0) 1.0 (0.4–2.4) 3.5 (1.2–28.7) 2.8 (1.1–11.7)	Age, parity, use of oral contraceptives	Cases diagnosed with borderline (serous or mucinous) tumours; study limited by incomplete information on powder use and small size; no significant association between method of powder use and risk for borderline tumours

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Chen *et al.* (1992), Beijing, China, 1984–86	112 women from Beijing Cancer Registry, with a mean age of 48.5 years; confirmation of diagnosis by laparotomy and pathological examination in all cases; 224 population-based controls selected first on basis of area of residence of cases and then randomly from census lists of all women within 1 year of age of identified case; matched by age; mean age, 49.0 years	Interviewer-administered questionnaire; information obtained on menstrual, obstetric, marital, medical, family and dietary histories as well as exposure to talc (perineally and occupationally); perineal exposure reported as yes/no	Use on perineum or lower abdomen	7	3.9 (0.9–10.6)	Education, parity	Age range of cases and controls not reported

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Harlow *et al.* (1992), Boston, MA, Massachusetts, USA, 1984–87	235 white women from 10 hospitals in metropolitan Boston area, aged 18–76 years; independent pathological confirmation of diagnosis; 239 population-based controls randomly selected from town registers; matched by age (±2 years), race, precinct of residence; no history of bilateral oopherectomy	In-person interviews; information collected on occupational history, medical and reproductive history, dietary history, tobacco smoking, hygienic practices including perineal exposure to talc; exposure to talc categorized by type of application, brand of powders, duration and frequency of use	'Any' perineal use of talc	114	1.5 (1.0–2.1)	Parity, education, marital status, religion, use of sanitary napkins, douching, age, weight	Odds ratio for women with >10 000 lifetime applications unchanged after excluding applications that occurred after tubal ligation or hysterectomy (odds ratio, 1.7; 95% CI, 1.0–3.0); significant increase in odds ratio for women with >10 000 lifetime applications observed after excluding use of talc during non-ovulatory periods and after surgical sterilization (odds ratio, 2.8; 95% CI, 1.4–5.4)
			Method of application				
			Sanitary napkins or underwear only	9	1.1 (0.4–2.8)		
			Partner or applications to diaphragm	20	1.2 (0.6–2.4)		
			Dusting on perineum	85	1.7 (1.1–2.7)		
			Frequency (no. per month)				
			None	121	1.0		
			<5	32	1.5 (0.8–2.7)		
			5–29	24	1.2 (0.6–2.2)		
			≥30	58	1.8 (1.1–3.0)		
			p for trend		0.046		
			Years of use				
			None	121	1.0		
			<10	14	1.2 (0.5–2.6)		
			10–29	49	1.6 (1.0–2.7)		
			≥30	51	1.6 (1.0–2.7)		
			p for trend		0.07		
			Total applications				
			None	121	1.0		
			<1000	18	1.3 (0.7–2.7)		
			1000–10 000	54	1.5 (0.9–2.4)		
			>10 000	42	1.8 (1.0–3.0)		
			p for trend		0.09		

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Rosenblatt *et al.* (1992), Baltimore, MD, USA, 1981–85	77 women admitted to Johns Hopkins Hospital as in-patients for treatment or diagnosis; diagnosed within 6 months of admission; residents of the USA; pathological confirmation of diagnosis; 46 hospital-based controls selected from female in-patients with no gynaecological or malignant conditions; matched *a posteriori* by age (±5 years), race, closest date of diagnostic admission	Questionnaire administered by telephone and in the hospital; information collected on genital and respiratory exposure to fibre-containing substances, such as talc; sources of genital exposure included contraceptive methods (diaphragm, condoms), dusting of perineum and sanitary products; sources of respiratory exposure included: use of face and/or body powders; residential or occupational exposure to fibre-containing substances, such as talc, asbestos, fiberglass; estimation of 'dose' by adding number of years of exposure from all sources	Genital fibre use *Method of application* Diaphragm use with powder Genital bath talc Sanitary napkin with talc exposure	67 14 22 21	1.0 (0.2–4.0) 3.0 (0.8–10.8) 1.7 (0.7–3.9) 4.8 (1.3–17.8)	Parity Parity, education No adjustment Highest weight, 1 year prior to diagnosis	Investigators encountered difficulty finding controls who met all of the matching criteria. For analysis, 46 matched sets, of which 31 sets had 2 cases and 1 control; limitations include small study size, broad definition of fibre exposure, limited information available on perineal exposure to talc

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Tzonou *et al.* (1993), Athens, Greece, 1989–91	189 women hospitalized for ovarian cancer surgery in 2 major cancer hospitals in Greater Athens, aged 75 years or under; histological confirmation of diagnosis; 200 hospital visitor controls (selected from visitors to patients hospitalized in the same wards as cases); not matched to cases by age	Questionnaire administered in hospital by medical residents; information collected on medical and reproductive histories, as well as personal, demographic and socioeconomic variables; qualitative assessment of talc exposure (yes/no use in the perineal region)	*Talc application in perineum* No Yes	 183 6	 1.0 1.1 (0.3–4.0)	Age, education, weight, age at menarche, menopausal status, age at menopause, parity, age at first birth, smoking status, alcohol use, coffee consumption, use of analgesics, use of tranquilizers or hypnotics, use of hair dyes	Study limited by very low prevalence of perineal talc use

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Purdie *et al.* (1995), Queensland, New South Wales, Victoria, Australia, 1990–93	824 incident cases diagnosed and registered in all major gynaecological-oncology treatment centres in 3 states, aged 18–79 years; independent pathological confirmation of diagnosis; 860 population-based controls selected randomly from electoral rolls, stratified by age and geographical region	Interviewer-administered standardized questionnaire in clinic (cases) or home (some cases, all controls); information collected on medical, reproductive, family and occupational histories, as well as dietary factors and history of talc use	Use of talc around the abdomen or perineum	[467] 56.7%	1.3 (1.0–1.5)	Parity; other potential confounders, e.g. contraceptive use, also considered	
Shushan *et al.* (1996), Israel, 1990–93	200 incident cases (164 invasive, 36 borderline) diagnosed and reported to Israel Cancer Registry, aged 36–64 years; histological confirmation of diagnosis; 408 population-based controls selected by random-digit dialing; matched by geographical area	Interviewer-administered standard questionnaire; information collected on reproductive history, use of oral contraceptives and fertility drugs, exposure to talc; exposure to talc stratified into 'never/seldom', 'moderate/a lot'	*Use of talc* Moderate/a lot	21	[1.97] ($p = 0.04$)	No control for confounding	Study limited by the very sparse information on talc use and the unavailability of adjusted results for the association between use of talc and the risk for ovarian cancer

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Chang & Risch (1997), metropolitan Toronto and southern Ontario, Canada, 1989–92	450 incident cases (primary, invasive and borderline); aged 35–79 years; histological confirmation of diagnosis; 564 population-based controls identified through provincial records of all homeowners, tenants and family members; randomly selected from same residential area; matched by age within 15-year age groups	Interviewer-administered questionnaire; information collected on menstrual and reproductive history, use of hormones and oral contraceptives, and use of talc; exposure to talc categorized on basis of 'any' exposure, type of exposure, frequency and duration of perineal application	'Any' exposure to talc	198	1.4 (1.1–1.9)	Age at interview, duration of oral contraceptive use, parity (number of full-term pregnancies), duration of lactation per pregnancy, history of tubal ligation or hysterectomy, family history of breast or ovarian cancer	Authors do not specify whether cases were identified through a cancer registry or some other reporting mechanism. Borderline significant trend observed with increasing duration of exposure to talc, but not with increasing frequency of exposure
			Type of exposure				
			Sanitary napkins	51	1.3 (0.9–2.0)		
			After bathing	172	1.3 (1.0–1.7)		
			Frequency of after-bath use (times/month)				
			None		1.0		
			<10	76	1.8 (1.2–2.7)		
			10–25	54	1.1 (0.7–1.7)		
			>25	41	1.0 (0.6–1.5)		
			Per 10 applications per month		0.9 (0.7–1.1)		
			Duration of after-bath use (years)				
			None		1.0		
			<30	60	1.7 (1.1–2.6)		
			30–40	71	1.4 (1.0–2.2)		
			>40	41	0.9 (0.5–1.4)		
			Per 10 years of use		1.1 (1.0–1.2)		

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Cook *et al.* (1997) Western Washington State, USA, 1986–1988	313 incident cases (234 invasive, 79 borderline) identified from records of Cancer Surveillance System of western Washington; white residents of three counties (King, Pierce, Snohomish), aged 20–79 years; no information on whether diagnosis was histologically confirmed; 422 white population-based controls selected by random digit-dialling (part of a larger control pool for several studies of cancer in women); matched by age	Structured in-person interviews; information collected on medical and reproductive histories, smoking habits, birth control methods and use of genital powders and deodorant sprays; exposure to genital powders assessed on the basis of 'any' lifetime exposure, method of use and cumulative lifetime exposure (days, months or lifetime applications)	*Lifetime perineal application*			Adjusted for age	
			None	154	1.0		
			Any	159	1.5 (1.1–2.0)	Adjusted for age	
			Exclusive use of powder for				
			Perineal dusting	55	1.8 (1.2–2.9)		
			Diaphragm storage	22	0.8 (0.4–1.4)		
			Dusting sanitary napkins	12	1.5 (0.6–3.6)		
			Deodorant spray	18	1.5 (0.8–3.0)	Adjusted for age and other methods of genital powder application	
			Any use of powder for				
			Perineal dusting	95	1.6 (1.1–2.3)		
			Diaphragm storage	46	1.0 (0.6–1.6)		
			Dusting sanitary napkins	38	0.9 (0.5–1.5)		
			Deodorant spray	40	1.9 (1.1–3.1)	Adjusted for age and other methods of genital powder application	
			Cumulative lifetime perineal dusting (days)				
			None	154	1.0		
			≤2000	20	1.8 (0.9–3.5)		
			2001–5000	24	1.6 (0.9–2.9)		
			5001–10 000	21	1.2 (0.6–2.4)		
			>10 000	28	1.8 (0.9–3.4)		

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Eltabbakh *et al.* (1998), Buffalo, NY, USA, 1982–96	'Study' group: 50 women admitted for treatment of primary extra-ovarian peritoneal cancer to Roswell Park Cancer Institute; histological confirmation of diagnosis; 'control' group: 466 women treated for primary ovarian cancer at same centre; pathological review of diagnosis	Self-administered, 44-item questionnaire completed at hospital admission	Perineal use of talc	224 (48.1%)	p=0.003	No control for confounding	'Cases for this study were women diagnosed with primary peritoneal cancers. Case definition excluded patients with diagnoses of peritoneal mesothelioma, borderline tumours of peritoneum or invasive ovarian cancer; no healthy controls enrolled in this study. 'Controls' were women diagnosed with primary epithelial ovarian cancer. Control definition excluded patients with diagnoses of non-epithelial ovarian cancer and ovarian cancer secondary to metastases from other sites.

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Godard *et al.* (1998), Montreal, Quebec, Canada, 1995–96	170 incident cases with primary invasive or borderline epithelial tumours, identified at two gynaecological clinics, aged 20–84 years; histological confirmation of diagnosis; 170 population-based controls selected by a modified random-digit dialling method; frequency-matched by age (±1 year), French Canadian ethnicity	Standardized 57-item questionnaire; telephone or in-person interviews conducted with cases, no information on how controls were interviewed; qualitative assessment of perineal talc exposure (ever/never)	'Ever' use of talc on perineum	[18] (10.6%)	2.5 (0.9–6.6)	Age at menarche, age at menopause, parity, age at first and last childbirth, duration of oral contraceptive use, age at last oral contraceptive use, tubal ligation, alcohol use, previous breast or abdominal surgery	

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Cramer *et al.* (1999), eastern Massachusetts and New Hampshire, USA, 1992–97	563 incident cases (including borderline tumours) identified through hospital tumour boards or statewide cancer registries; age range not provided; histological confirmation of diagnosis for all cases; 523 population-based controls selected by random-digit dialling and through annual listings of names, ages and addresses of all Massachusetts residents (women over the age of 60 years); frequency-matched by age (±4 years), location of residence	In-person interviews using standardized questionnaire; information collected on medical and reproductive histories, family history and personal habits; multiple questions on potential routes of talc exposure (non-genital, genital, husband's use), brands used, age at first use, duration and frequency of use	No genital exposure	411	1.0	Age, study site, parity, oral contraceptive use, body mass index, family history of breast or ovarian cancer, history of tubal ligation	
			Any genital exposure	152	1.6 (1.2–2.1)		
			Method of use				
			No use	312	1.0		
			Non-genital areas	99	1.1 (0.8–1.5)		
			Dusting perineum	71	1.5 (1.0–2.2)		
			Dusting sanitary napkins	20	1.5 (0.7–3.1)		
			Dusting underwear	8	1.2 (0.4–3.6)		
			More than one method	53	2.2 (1.3–3.6)		
			Frequency (uses/month)				
			None	312	1.0		
			<30	64	2.2 (1.4–3.6)		
			30–39	59	1.7 (0.8–1.8)		
			≥40	23	1.7 (0.8–3.1)		
			Duration of use (years)				
			None	312	1.0		
			<20	55	1.9 (1.2–3.0)		
			20–30	32	1.3 (0.8–2.3)		
			>30	59	1.4 (0.9–2.3)		

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Cramer *et al.* (1999) (contd)			*Total no. of applications*				
			None	312	1.0		
			<3000	51	1.8 (1.1–3.0)		
			3000–10 000	36	1.4 (0.8–2.4)		
			>10 000	59	1.4 (0.9–2.2)		
			p for trend		0.16		
			Total no. of applications (censored analysis)				Censored analysis excludes talc applications that occurred during non-ovulatory years or after hysterectomy or tubal ligation. Includes non-genitally exposed women.
			None	312	1.0		
			<3000	59	1.5 (1.0–2.4)		
			3000–10 000	51	1.7 (1.1–2.8)		
			>10 000	36	1.8 (1.0–3.2)		
			p for trend		0.02		

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Wong *et al.* (1999) Buffalo, NY, USA, 1982–92	462 incident cases admitted for treatment of primary extra-ovarian peritoneal cancer to Roswell Park Cancer Institute, mean age, 54.9 years; histological confirmation of diagnosis; 693 hospital-based controls treated for non-gynaecological malignancies at same cancer centre; mean age, 54.9 years; frequency-matched to cases by age at diagnosis (±5 years)	Self-administered, 44-item questionnaire completed at hospital admission; information collected on medical, social, family, dietary and occupational histories; method of talc use (never, sanitary napkin, genital/thigh area, both) assessed and duration of use	*Method of use* Never Sanitary napkin Genital or thigh area Both *Duration of use (years)* None 1–9 10–19 ≥20	 241 13 157 51 241 39 49 101	 1.0 0.9 (0.4–2.0) 1.0 (0.8–1.3) 1.1 (0.7–1.7) 1.0 0.9 (0.6–1.5) 1.4 (0.9–2.2) 0.9 (0.6–1.2)	Age, parity, oral contraceptive use, smoking, family history of ovarian cancer, age at menarche, menopausal status, income, education, geographical location, history of tubal ligation or hysterectomy	Case population largely that reported by Eltabbakh *et al.* (1998); 32 cases, 39 controls did not recall duration of use.

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Ness *et al.* (2000), eastern Pennsylvania, southern New Jersey, Delaware, USA, 1994–1998	767 incident cases identified at 39 hospitals in the Delaware Valley region; aged 20–69; diagnosis within 6 months prior to interview; pathological review of a random subset of cases (n = 120) 1367 population-based controls identified through random digit dialing (≤65 years of age) and Health Care Financing Administration lists (65–69 years of age); frequency matched by age and location of residence	Standardized in-person interviews; information collected on sexual activity, use of contraceptives, menstrual and reproductive history, and history and duration of talc use (genital, non-genital applications, exposure via male sexual partners)	*Method of use* Never Feet, arms, breasts Genital/rectal Sanitary napkin Underwear Diaphragm/ cervical cap Male partner *Duration of use (years)* Never <1 1–4 5–9 ≥10	 349 335 161 77 70 10 56 401 17 76 40 233	 1.0 1.4 (1.1–1.6) 1.5 (1.2–2.0) 1.6 (1.1–2.3) 1.7 (1.2–2.4) 0.6 (0.3–1.2) 1.0 (0.7–1.4) 1.0 2.0 (1.0–4.0) 1.6 (1.1–2.3) 1.2 (0.8–1.9) 1.2 (1.0–1.5)	Age, parity, race, family history of ovarian cancers, oral contraceptive use, tubal ligation, hysterectomy, lactation	Risk for ovarian cancer compared with 50 women with primary peritoneal cancers; no control for confounding; analysis of duration examined risk for cases reporting use of talc on the feet, genital and rectal areas.

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Langseth & Kjaerheim (2004), Norway, 1953–99	35 (invasive and borderline tumours) selected from cohort of 4247 female pulp and paper workers; cohort follow-up, 1953–99; histological review and confirmation of diagnosis; 121 selected from the cohort by incidence density sampling; matched by birth (year ±2 years); controls had no ovarian cancer and had intact ovaries	In-person interviews conducted at mills or by telephone; information collected on occupational history, household exposure to asbestos, menstrual and reproductive history, hereditary risk of cancer, as well as talc use on sanitary napkins, underwear or diapers or by husband in genital area.	'Ever' use of talc for personal hygiene	12	1.2 (0.4–3.2)	Adjusted for possible confounders, but not explicitly stated	Nested case–control study conducted in a cohort study of 10 pulp and paper mills; many missing values among proxy respondents

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Mills *et al.* (2004), central California, USA, 2000–01	249 incident cases from 22 counties diagnosed in two regional cancer registries, using rapid case ascertainment procedures; histological confirmation of diagnosis for a subset of cases; 1105 population-based controls identified by random-digit dialling; frequency-matched by age, race, ethnicity	Telephone interview to obtain information on medical history, menstrual and reproductive history, family history of cancer, history of perineal talc exposure (frequency, duration and calendar years of use); 'cumulative' use calculated by multiplying frequency (categorical variable) by duration in months	*Perineal use of talc* Never Ever *Frequency of use* Never <1/week 1–3/week 4–7/week *p* for trend *Duration of use (years)* Never ≤3 4–12 13–30 >30 *p* for trend *Cumulative use* Never 1st quartile (lowest) 2nd quartile 3rd quartile 4th quartile (highest) *p* for trend	 143 106 143 34 31 41 143 18 32 29 21 143 18 28 34 20 	 1.0 1.4 (1.0–1.9) 1.0 1.3 (0.9–2.1) 1.6 (0.7–1.8) 1.7 (1.1–2.6) 0.015 1.0 1.0 (0.6–1.8) 1.9 (1.2–3.0) 1.5 (0.9–2.3) 1.2 (0.7–2.1) 0.045 1.0 1.0 (0.6–1.8) 1.8 (1.1–3.0) 1.7 (1.1–2.7) 1.1 (0.6–1.8) 0.051	Age, race/ethnicity, duration of oral contraceptive use, breastfeeding. Additional covariates considered to be potential confounders included family history of breast or ovarian cancer, parity, history of pregnancy, body mass index, hysterectomy, tubal ligation, duration of post-menopausal use of hormones.	Cumulative use calculated as frequency (categorical weighting from 0–3) multiplied by duration.

CI, confidence interval

to talc by way of contraceptives, perineal hygiene or surgery. Ninety-two cases (42.8%) and 61 controls (28.4%) reported a history of regular use of talc as a dusting powder to the perineum, on sanitary napkins or on both. After adjustment for parity (yes/no) and menopausal status (pre-/post-), a significant association was found between 'any perineal use' of talcum powder and the risk for ovarian cancer (odds ratio, 1.9; 95% CI, 1.3–2.9). This association was attenuated but still significant after adjustment for additional potential confounders, including religion, marital status, level of education, weight, age at menarche, parity (number of children), oral contraceptive use, menopausal use of hormones and tobacco smoking (adjusted odds ratio, 1.6; 95% CI, 1.0–2.5). A single type of perineal exposure to talc (either as a dusting powder to the perineum or on sanitary napkins) was associated with a borderline significantly increased risk for ovarian cancer (odds ratio, 1.6; 95% CI, 1.0–2.5) after adjustment for parity and menopausal status, while a history of both types of perineal exposure was associated with a significant increase in risk (adjusted odds ratio, 3.3; 95% CI, 1.7–6.4). No association was seen between other potential sources of exposure to talc (pelvic surgery, use of condoms, use of diaphragm or using talc for diaphragm storage) and the risk for ovarian cancer. In addition, the results were essentially unchanged after excluding women who had had a tubal ligation or hysterectomy (odds ratio, 2.8; $P < 0.003$), although the authors noted that these surgical procedures are usually performed at mid-life when substantial exposure to talc may already have occurred. The distribution of tumour histologies was similar for exposed and unexposed cases; 53.7% of tumours were classified as serous among the unexposed cases and 48.9% among the exposed cases with 'any' perineal use of talc. [Limitations of this report include the lack of information on duration and frequency of talc use. In addition, participation rates among the controls were quite low (50%), although the authors noted in a secondary analysis that, when cases were matched to the first control selected (i.e. 100% participation), a positive association was also found (odds ratio, 2.44; $P < 0.05$).]

Hartge *et al.* (1983) published a brief report of a study conducted between 1974 and 1977 in the Washington DC (USA) area. The study included 197 cases treated for pathologically confirmed epithelial ovarian cancer at participating hospitals and 197 controls treated at the same hospitals for conditions other than pregnancy, malignancies and gynaecological or psychiatric diseases. Controls were frequency-matched to cases by age, race and hospital. Interviews were conducted in the hospital for controls and at home for most cases to collect information on reproductive and sexual history, medical history, drug use and other exposures. Questions on exposure to talc were added after the study began. As a result, the analysis included only 135 cases and 171 controls with information on exposure to talc. Sixty-seven cases [49.6%] and 100 controls [58.5%] reported 'any' use of talc (including non-genital uses), while seven cases [5.2%] and three controls [1.8%] reported genital use of talc (including use on genitals, on sanitary napkins or on underwear). No association was observed between 'any' use of talc and the risk for ovarian cancer (odds ratio, 0.7; 95% CI, 0.4–1.1). This estimate was unchanged after adjustment for race, age and pregnancy. A non-significant positive association was found between genital use of talc and the risk for ovarian cancer (odds

ratio, 2.5; 95% CI, 0.7–10.0). [Limitations of this study included its small size and the low prevalence of genital use of talc, the lack of information on its duration and frequency and age at first use, the lack of control for other potential confounders and the increased potential for selection bias due to different interviewing protocols for cases and controls. In addition, no information was given in this brief report on the methods used in the analysis to control for confounding.]

Whittemore *et al.* (1988) analysed the association between perineal use of talc and the risk for invasive epithelial ovarian cancer among 188 cases and 539 controls in the San Francisco Bay area (CA, USA). Cases were residents of northern California, aged 18–74 years, who had been diagnosed with an invasive ovarian tumour between January 1983 and December 1985 at one of eight hospitals. Controls were either selected from among women who had been hospitalized for a non-cancerous condition at one of these eight hospitals or were identified from the population using random-digit dialling. Women in each control group were matched to each case by age (within 5 years) and race (white, black, other), plus hospital and date of admission (within 3 months) for the hospital controls ($n = 280$) and telephone area code and prefix for the population-based controls ($n = 259$). Structured interviews were conducted in the homes of participants to obtain information on the history, frequency and duration of perineal use of talc, medical history and additional covariates of interest (menstrual and reproductive histories, family history and environmental exposures, such as consumption of alcohol, coffee and tobacco). Of 317 eligible cases, eight (2.5%) were excluded due to physician refusal, 30 (9.5%) due to patient refusal, 44 (13.9%) due to death or incapacitating illness and 47 (14.8%) due to non-invasive tumours, which left 188 (59.3%) for inclusion in the analysis. Among the controls, 68% of the women identified as eligible hospital controls ($n = 354$) and 71% of the women identified by telephone as eligible population-based controls ($n = 329$) agreed to participate. After excluding controls matched to cases with bordeline tumours, 280 hospital controls and 259 population controls were included in the analysis (Wu *et al.*, 1988). Exposure to talc was categorized by type of application (perineum only, sanitary pads only, diaphragm only, any two types of application or all three types of application), duration of use before tubal ligation (none, 1–9 years, ≥ 10 years, unknown) and frequency of use (none, 1–20 applications per month, > 20 applications per month, unknown). Conditional logistic regression was used to calculate the odds ratio for each exposure and to test for trend. Ninety-seven cases (51.6%) and 247 controls (45.8%) reported previous use of talcum powder on the perineum to yield an odds ratio of 1.40 ($P = 0.06$) after adjustment for parity. Since the odds ratios were similar when hospital-based and population-based controls were analysed separately, analyses using the combined group of controls were reported. After adjustment for parity and oral contraceptive use, the odds ratio for use of talc on the perineum only was 1.5 (95% CI, 0.8–2.6). No significant associations were observed with either individual or multiple types of perineal talc use, including the combination of use on the perineum, sanitary napkins and a diaphragm (odds ratio, 1.4; 95% CI, 0.9–2.0 for any two types of use versus 0.4; 95% CI, 0.0–2.9 for all three types combined). No

significant trend was observed with duration of talc use on the perineum before tubal ligation or hysterectomy. Odds ratios were 1.6 (95% CI, 1.0–2.6) for 1–9 years of exposure and 1.1 (95% CI, 0.7–1.7) for more than 10 years of exposure. A non-significant trend of increased risk with increasing frequency of perineal use of talc was observed, with an overall odds ratio of 1.3 (95% CI, 0.9–1.9; $P = 0.19$) for 30 applications per month. When stratified by history of perineal use of talc (yes/no) and history of tubal ligation or hysterectomy (yes/no), women who had used talc perineally and but had not undergone surgery for sterilization had the highest risk for ovarian cancer (odds ratio, 1.3; 95% CI, 0.9–2.0). [Limitations of this study included the lack of information on talc use.]

Booth *et al.* (1989) reported results of a hospital-based case–control study of the risk for ovarian cancer conducted in 15 hospitals in London and Oxford (United Kingdom) from October 1978 to February 1983. Women aged 65 years or under at diagnosis and who were diagnosed within 2 years of the study interview were eligible for inclusion. A total of 280 potential cases were identified, interviewed and classified with respect to tumour histology. After excluding 45 women, 235 cases were included in the analysis. A total of 451 controls with the same age distribution as the cases were selected from the same 15 hospitals. Controls had a range of admission diagnoses; gastrointestinal disease ($n = 105$) and bone or joint disease ($n = 70$) were the most common. Women were excluded as controls if they had a history of bilateral oophorectomy or if they had a condition related to oral contraceptive use or other reproductive factors. Participation rates were not provided. Interviewers used a standard questionnaire to obtain information on reproductive and menstrual history, as well as exposure to exogenous estrogens, cigarettes and talc. Talc exposure was categorized according to the frequency of perineal use (never, rarely, monthly, weekly or daily) and whether it was used for storage of a diaphragm. Multiple logistic regression adjusted for age and socioeconomic status was conducted. Fifty-seven cases [24.3%] and 77 controls [17.1%] reported a history of weekly use of talc in the genital area, while 71 cases [30.2%] and 139 controls [30.8%] reported daily use. Weekly genital use of talc was associated with a significantly increased risk for ovarian cancer (odds ratio, 2.0; 95% CI, 1.3–3.4), while daily use was associated with a non-significant increase in risk (odds ratio, 1.3; 95% CI, 0.8–1.9), after adjustment for age and socioeconomic status. The *p*-value for trend with increasing frequency of use was of borderline significance ($P = 0.05$). The percentage of diaphragm users who reported storing their diaphragm in talc was not significantly different between the cases (86%) and controls (81%). [Limitations of this hospital-based study included the limited information on talc use. As participation rates were not provided, the possibility of selection bias is difficult to evaluate. Although covariates such as oral contraceptive use or parity were available, it was not explicitly stated if they were evaluated.]

Harlow and Weiss (1989) conducted a study of perineal use of powder and the risk for borderline ovarian cancer in western Washington State, USA. Cases were 116 Caucasian women aged 20–79 years who had been diagnosed with borderline serous or mucinous epithelial ovarian cancer between 1980 and 1985, and who were identified by International Classification of Diseases-0 codes obtained from a population-based

cancer-reporting system. Controls were identified from the same counties of residence by random-digit dialling. A total of 158 women with a similar age distribution to the cases and who had not undergone a bilateral oophorectomy were included in the analysis. Cases and controls were interviewed in-person to obtain information on reproductive, sexual and medical histories, as well as on perineal exposure to talc (through multiple open-ended questions about the history of powder use of the participant). Among all eligible cases and controls identified for the study, 68% of the cases and 74% of the controls were interviewed. The authors controlled for age (20–39, 40–59 or 60–79 years), parity (nulliparous or parous) and oral contraceptive use (ever/never). Exposure to talc was broadly categorized as 'any perineal use of dusting powders' (after bathing, on sanitary napkins or for diaphragm storage) and further subcategorized according to method of use (diaphragm storage only, after bathing only, sanitary napkins only, after bathing and on sanitary napkins and specific combinations of the various methods) and type of powder used (cornstarch only, baby powder only, talc unspecified (no combined use), deodorizing powder only or combinations of powders). Forty-nine cases [42.2%] and 64 controls [40.5%] reported a history of 'any perineal exposure to powder' to yield an odds ratio of 1.1 (95% CI, 0.7–2.1). When analysed by the type of powder used, the risk for borderline ovarian cancer was elevated only for perineal use of deodorizing powder alone (odds ratio, 3.5; 95% CI, 1.2–28.7) or in combination with other powders (odds ratio, 2.8; 95% CI, 1.1–11.7). No association was noted for the use of baby powder alone (odds ratio, 0.8; 95% CI, 0.4–1.9) or for combined use (odds ratio, 0.9; 95% CI, 0.5–2.0) or for other unspecified use of talc (odds ratio, 1.0; 95% CI, 0.4–2.4). No significant association was found between risk for borderline tumours and any individual method of powder use, including use after bathing, on sanitary napkins or for diaphragm storage. The authors reported no increase in risk with increasing number of days of powder use, although the data were not provided in the paper. [Limitations of this study included the incomplete information on powder use and its small size.]

Chen *et al.* (1992) (described in detail in Section 2.1.2) conducted a case–control study in Beijing, China, of several risk factors for epithelial ovarian cancer that included perineal exposure to talc (yes/no use of dusting powder to the lower abdomen or perineum for 3 or more months). The analysis was carried out on 112 newly diagnosed cases identified between 1984 and 1986 through the Beijing Cancer Registry and 224 age-matched community controls (two controls per case). Seven cases [6.3%] and five controls [2.2%] reported use of talc-containing powders which resulted in an odds ratio of 3.9 (95% CI, 0.9–10.6) after adjustment for education and parity. [The Working Group noted the incomplete ascertainment of cases of ovarian cancer due to the nature of the cancer-reporting system in China, the large number of cases that were excluded due to death and the exclusion of controls who had a history of serious health problems (which may have resulted in selection bias), the limited information on perineal use of talc, the lack of adjustment for other potential confounding variables, the small number of cases and the low prevalence of talc use.]

Harlow *et al.* (1992) analysed perineal exposure to talc and the risk for ovarian cancer among 235 cases and 239 controls in the Boston, MA metropolitan area (USA). Cases were diagnosed with ovarian cancer between June 1984 and September 1987 at one of 10 Boston hospitals and controls were identified from town registers listing the name, age and address of all residents in Massachusetts. All cases were Caucasian women aged 18–76 years at diagnosis and were similar to the controls with respect to race, age and area of residence. Of 397 cases identified during the study period, 31% were not interviewed due to physician and/or patient refusal, death or change of address. After excluding women whose cancer diagnosis was not confirmed by an independent pathology review [9.4% of eligible cases], 235 women were included in the analysis. A total of 526 women were contacted as potential controls. Of these, 239 [45.4%] were interviewed, 25% could not be reached, 10% reported a previous bilateral oophorectomy and 19% did not wish to participate in the study. In-person interviews were conducted with cases and controls to obtain information on occupational history, medical and reproductive histories, dietary history, cigarette smoking and hygienic practices (use of douches, types of sanitary protection used, perineal exposure to talc). Exposure to talc was categorized on the basis of 'any' exposure, the method of application (dusting on sanitary napkins and/or underwear, via partner or application to diaphragm, dusting on perineum), the brand used, age at first use, duration and frequency of use. Total lifetime exposure to talc was estimated by cumulating the frequency of exposure and years of use to arrive at a summary measure of the total number of applications (< 1000, 1000–10 000, > 10 000). Covariates evaluated as potential confounders included age, education, marital status, religion, weight, use of oral contraceptives and parity; of these, age, education (< 12 years, > 12 years), marital status (never/ever), religion (Jewish, non-Jewish), weight (< 140 lb, ≥ 140 lb) and parity (0, 1–2, > 2) were included in all multivariable models. A history of 'any' perineal exposure to talc-containing powders was reported by 48.5% of cases and 39.3% of controls to yield an odds ratio of 1.5 (95% CI, 1.0–2.1). When the method of application was examined, only direct application to the perineum as a dusting powder was associated with a significant increase in risk (odds ratio, 1.7; 95% CI, 1.1–2.7). Women who reported at least 30 applications of talcum powder per month had a significant increase in risk (odds ratio, 1.8; 95% CI, 1.1–3.0), while women with fewer applications per month did not. A significant positive trend was seen with number of monthly applications ($P = 0.046$). Women with at least 10 years of perineal exposure had a borderline significant increase in risk (odds ratio, 1.6; 95% CI, 1.0–2.7) and the *p*-value for trend was also of borderline significance ($P = 0.07$). Analyses stratified by age at first use indicated that women who first used talc genitally before the age of 20 years had the highest risk (odds ratio, 1.7; 95% CI, 1.1–2.7); those stratified by years since last use suggested that women with the most recent perineal use of talc (within the previous 6 months) had the highest risk (odds ratio, 2.3; 95% CI, 1.3–4.0). In an analysis stratified by use before versus after 1960, women who reported some perineal use of talc before 1960 had a significantly elevated risk for ovarian cancer (odds ratio, 1.7; 95% CI, 1.1–2.7), while women with exclusive genital use of talc after 1960 did not (odds ratio, 1.1;

95% CI, 0.6–2.1). Women who had used more than 10 000 lifetime applications had a borderline significant increase in risk (odds ratio, 1.8; 95% CI, 1.0–3.0). This was unchanged after excluding applications that occurred after tubal ligation or hysterectomy (odds ratio, 1.7; 95% CI, 1.0–3.0). However, when use of talc during non-ovulatory periods and after surgical sterilization was excluded, the increase in risk associated with more than 10 000 lifetime applications was significant (odds ratio, 2.8; 95% CI, 1.4–5.4). In analyses of each histological type and grade, the strongest associations were seen for endometrioid tumours (odds ratio, 2.8; 95% CI, 1.2–6.4) and tumours of borderline invasiveness (odds ratio, 2.4; 95% CI, 1.2–4.5) (Table 2.4).

Rosenblatt *et al.* (1992) conducted a hospital-based case–control study among 77 women who were hospitalized at Johns Hopkins Hospital in Baltimore, MD (USA) for ovarian cancer (cases) and 46 who were hospitalized for non-gynaecological, non-malignant conditions (controls). The cases were newly diagnosed with pathologically confirmed epithelial ovarian cancer between 1981 and 1985, the majority of whom were aged 40–69 years. Of 140 eligible cases, 108 (77.1%) were interviewed. Thirteen were subsequently excluded because no control was identified and 18 were excluded for an unspecified reason. Controls were matched to cases by age, race and date of diagnostic admission. Information on genital and respiratory exposure to fibre-containing substances (talc, asbestos and fibreglass), as well as potential confounders, was collected using a structured questionnaire which was administered in the hospital and by telephone. Covariates that were considered to be potential confounders included tobacco use, 'ovulatory time period', parity, family history of cancer, obesity, education, education of husband, previous history of cancer, marital status, religion and the use of oral contraceptives and other methods of contraception. Sources of genital fibre exposure (yes/no) included diaphragm use and dusting of either the perineum or sanitary napkins with talcum powder. Potential sources of respiratory fibre exposure (yes/no) included use of face or body powders containing talc, insulation installed at residence and living in the vicinity of or employment in a fibre-emitting industry (such as shipyard, asbestos or talc mine, asbestos/talc/fibreglass processing plant). A large percentage of both the cases (87%) and controls (88%) reported exposure to genital fibre, with an odds ratio of 1.0 (95% CI, 0.2–4.0) after adjustment for parity. A long duration of genital fibre use (median duration, ≥ 37.4 years) was associated with a borderline significant increase in the risk for ovarian cancer (odds ratio, 2.4; 95% CI, 1.0–5.8) after adjustment for religion. Odds ratios were also calculated for genital use of bath talc (odds ratio, 1.7; 95% CI, 0.7–3.9), use of talc on sanitary napkins (odds ratio, 4.8; 95% CI, 1.3–17.8) and use of talc on a diaphragm (odds ratio, 3.0; 95% CI, 0.8–10.8). No association was observed between risk for ovarian cancer and history of previous gynaecological or abdominal surgery that may have resulted in peritoneal exposure to talc. [Limitations of this study included the very small number of cases and controls, the broad definition of fibre exposure used in certain exposure variables and the limited information on perineal exposure to talc.]

Tzonou *et al.* (1993) conducted a hospital-based case–control study of risk factors for epithelial ovarian cancer in the Greater Athens region of Greece. The cases were 189 women

Table 2.4. Perineal talc use and ovarian cancer risk: by tumour histology

References	No. of cases	Histology	Relative risk[a] (95% CI)
Harlow *et al.* (1992)	60	Serous[b]	1.4 (0.9–2.2)
	17	Mucinous	1.2 (0.6–2.5)
	18	Endometrioid	2.8 (1.2–6.4)
Chang & Risch (1997)	254	Serous[b]	1.3 (1.0–1.9)
	80	Mucinous	1.6 (1.0–2.6)
	74	Endometrioid	1.7 (1.0–2.8)
Cook *et al.* (1997)	131	Serous	1.7 (1.1–2.5)
	43	Mucinous	0.7 (0.4–1.4)
	36	Endometrioid	1.2 (0.6–2.3)
Cramer *et al.* (1999)	229	Serous invasive	1.7 (1.2–2.4)
	83	Mucinous	0.8 (0.4–1.4)
	130	Endometrioid/clear cell	1.0 (0.7–1.6)
Wong *et al.* (1999)	136	Serous	1.2 (0.7–2.1)
	11	Mucinous	1.5 (0.6–4.0)
	21	Endometrioid	1.4 (0.7–2.7)
Gertig *et al.* (2000)	76	Serous invasive	1.4 (1.0–1.9)
Mills *et al.* (2004)	42	Serous invasive	1.8 (1.1–2.8)
	10	Mucinous invasive	2.6 (0.9–7.4)
	14	Endometrioid	1.3 (0.6–2.6)

CI, confidence interval
[a] Any or ever use of talc
[b] Includes borderline and invasive serous tumours

under 75 years of age who underwent surgery for ovarian cancer at one of two cancer hospitals in Athens between June 1989 and March 1991. The controls were 200 women under 75 years of age who were residents of Greater Athens and who visited patients hospitalized in the same wards as the cases during the study period. Ninety per cent of the eligible cases and 94% of the eligible controls agreed to participate. In-hospital interviews were conducted to collect information on a range of demographic, socioeconomic and reproductive factors, as well as information on exposure to hair dyes, analgesics, tranquilizers and talc. Exposure to talc was assessed qualitatively as 'yes/no' application of talc in the perineal region. In multivariable analyses, models were adjusted for age in 5-year groups, education, weight, age at menarche, menopausal status, age at menopause, parity, age at first birth, tobacco smoking status, alcohol use, coffee consumption and the other exposures of interest (use of analgesics, tranquilizers and hair dyes). Application of talc to the perineal region was reported by six cases [3.2%] and seven controls [3.5%] to yield an odds ratio of 1.1 (95% CI, 0.3–4.0) after adjustment for the potential confounders. [Limitations of this hospital-based case–control study included the very low prevalence of perineal use of talc.]

Purdie *et al.* (1995) conducted a case–control study among women in the three most populous Australian states—Queensland, New South Wales and Victoria. Cases were women, aged 18–79 years, who had been diagnosed with epithelial ovarian cancer between August 1990 and December 1993 at gynaecological oncology treatment centres in one of these three regions. Women were excluded if they had a metastatic tumour, were outside the eligible age range, could not be contacted, were too ill or were incapable of completing the questionnaire in conjunction with a trained interviewer (because of language difficulties or psychiatric conditions). Each case was confirmed by an independent pathological review of tissue specimens. Of 1116 cases identified during the study period, 201 (18%) were ineligible (e.g. due to a non-ovarian primary cancer or age at diagnosis). Among the 915 eligible cases, 824 (90%) agreed to participate and were interviewed. Reasons for non-participation included death before interview (50 cases), patient refusal (34 cases) and physician refusal (seven cases). Controls were identified from the electoral roll and were similar to the cases in age distribution and area of residence. Women were excluded as a control if they had a history of ovarian cancer or bilateral oophorectomy, could not be reached or could not complete the questionnaire. Among 1527 potential controls identified from the electoral roll, 1178 were located and found to be eligible (77%). Of these, 860 agreed to participate in the study (73% of the eligible controls). Reasons for ineligibility among the controls included failure to locate the individual (192), inability to complete the questionnaire due to language difficulties, a psychiatric condition, illness or death (105), previous bilateral oophorectomy (48) and age (four). Trained interviewers used a standardized questionnaire to collect information on medical, reproductive, family and occupational histories, as well as data on dietary factors and history of talc use. Questionnaires were administered face-to-face either in the clinic (for cases) or in the home of participant (for some cases and all controls). Covariates evaluated as potential confounders included parity, hysterectomy, tubal ligation, duration

of oral contraceptive use, age, education, body mass index, tobacco smoking status, family history of cancer and multiple menstrual and reproductive factors. Talc use around the abdomen or perineum was reported by 56.7% of cases and 52% of controls to yield an odds ratio of 1.3 (95% CI, 1.0–1.5) after adjustment for parity. Although enrolment in the electoral roll is mandatory in Australia, the authors determined that 28 cases [3.4%] had never enrolled and the enrolment status could not be confirmed for 46 cases [5.6%]. The results did not change when the analyses were limited to cases with confirmed enrolment in the electoral role.

Green *et al.* (1997) evaluated the association between tubal ligation or hysterectomy and the risk for ovarian cancer using the Australian study population described by Purdie *et al.* (1995). [The analysis by Green *et al.* (1997) used the same number of cases but five fewer controls than Purdie *et al.* (1995).] Duration of talc use was calculated as age at first reported use until age at occurrence of the earliest of any of the following events: surgical sterilization, reported last use of talc, diagnosis or interview. A modest increase in risk for ovarian cancer was observed with peritoneal use of talc (odds ratio, 1.3; 95% CI, 1.1–1.6). Neither duration of talc use nor age at first use were associated with risk for ovarian cancer, although the relative risks (95% CI) were not provided and the duration categories evaluated were not specified. When compared with women with no history of genital exposure to talc and patent fallopian tubes, women with a history of talc use and no history of surgical sterilization had the highest risk for ovarian cancer (odds ratio, 1.3; 95% CI, 1.0–1.7), while women with a history of tubal ligation or hysterectomy and no talc use had the lowest risk (odds ratio, 0.6; 95% CI, 0.5–0.8). [The primary limitation of this study was the restricted information on perineal use of talc.]

Shushan *et al.* (1996) examined the association between exposure to fertility drugs and the risk for ovarian cancer among 200 cases of epithelial ovarian cancer (164 invasive and 36 borderline) and 408 controls. All participants were living in Israel and were 36–64 years of age at enrolment into the study. Cases were identified through the Israel Cancer Registry from January 1990 to September 1993. Among 287 women who met the eligibility criteria (histologically confirmed diagnosis, cancer diagnosed and reported during study period, born between 1929 and 1957 and alive at time of interview), 87 (30.3%) were excluded because of inability to locate the patient or physician (25%), illness (1%), refusal by the physician (1%) or refusal by the patient (3%). Controls were identified by random-digit dialling and were matched to the cases by geographical area. Women were eligible to be included as a control if they were born in the same period as the cases. Potential controls were excluded if they had a history of bilateral oophorectomy (1%). Of 2072 telephone calls that successfully reached a household member, approximately half of the households [47.8%] contacted had a potentially eligible woman who was at home. Of these, 16.2% refused to participate and 10.7% were excluded because the woman did not speak Hebrew. Trained interviewers administered a standard questionnaire to all cases and controls. The questionnaire collected detailed information on reproductive history, use of oral contraceptives and fertility drugs, as well as exposure to talc (never/seldom, moderate/a lot). Although the main association of interest was use

of fertility drugs and the risk for ovarian cancer, the authors reported that 21 cases (10.5%) and 23 controls (5.6%) had a history of moderate or frequent use of talc, which yielded an unadjusted odds ratio of [1.97] ($P = 0.04$). [Limitations of this study included the very sparse information on talc use and the unavailability of adjusted results for the association between use of talc and the risk for ovarian cancer.]

Chang and Risch (1997) analysed the association between perineal use of powder and the risk for ovarian cancer among 450 cases and 564 population controls from metropolitan Toronto and southern Ontario, Canada. Cases were diagnosed between November 1989 and October 1992 and were between the ages of 35 and 79 years at entry into the study. Of 631 cases identified during the study period, 71.3% (450) were interviewed and included in the analysis. Reasons for non-participation included death (8.7%), physician refusal (4.6%), severe illness (4.8%), loss to follow-up (2.7%) and patient refusal (7.9%). Potential controls were identified through records of the Ontario Ministry of Finance based on their residence and age, were matched to cases within 15-year age groups and were excluded from the study if they had a history of bilateral oophorectomy more than 1 year before entry into the study. Among 873 eligible controls identified, 309 [35.4%] did not participate. Reasons included participant refusal (30.2%), illness (1.9%) or loss to follow-up (3.2%). Interviewers administered a standard questionnaire during an in-home interview to obtain information on the history, frequency and duration of use of talcum and cornstarch powder, as well as multiple medical and reproductive covariates of interest. Talc exposure was categorized on the basis of 'any' exposure in the perineal area, on the method of application (directly to the perineum after bathing or showering, dusting on sanitary napkins), on the frequency of application (< 10, 10–25, > 25 applications per month) and on the duration of exposure (< 30, 30–40, > 40 years of use). Multiple logistic regression was used in the analyses, with adjustment for age, duration of oral contraceptive use, parity (defined as the number of full-term pregnancies), duration of lactation for each pregnancy, history of tubal ligation or hysterectomy and family history of breast or ovarian cancer. Forty-four per cent of cases and 36% of controls reported 'any' talc use in the perineal area to yield an odds ratio of 1.4 (95% CI, 1.1–1.9). Among the specific types of talc exposure, application to the perineum after bathing was associated with a borderline significant increase in risk (odds ratio, 1.3; 95% CI, 1.0–1.7), while application on sanitary napkins (a less common use in this study population) was associated with an elevated but non-significant increase in risk (odds ratio, 1.3; 95% CI, 0.9–2.0). A borderline significant trend was seen with increasing duration of exposure to talc (odds ratio per 10 years of exposure, 1.1; 95% CI, 1.0–1.2), but not with increasing frequency of exposure. An analysis of duration by category (< 30, 30–40, > 40 years) did not suggest a dose–response relationship (odds ratios of 1.0; 1.7; 95% CI, 1.1–2.6; 1.4; 95% CI, 1.0–2.2 and 0.9; 95% CI, 0.5–1.4, respectively). Use of cornstarch in the perineal area, either alone or in conjunction with occasional talc, was not associated with the risk for ovarian cancer, although prevalence of use was low (less than 2% of subjects). To evaluate exposure pre- and post-1970, as well as exposure pre- and post-tubal ligation or hysterectomy, the authors assumed that participants initiated

perineal use of after-bath talc at the age of 20 years. A similar, non-significantly elevated, risk for ovarian cancer was seen for use pre- and post-1970. A higher odds ratio was seen for use of after-bath talc before tubal ligation or hysterectomy (odds ratio, 1.1; 95% CI, 1.0–1.2) than for use after these surgical procedures (odds ratio, 1.0; 95% CI, 0.8–1.3). These estimates did not change when different starting ages, between 15 and 24 years, were used in the analysis. The authors also evaluated the association between perineal use of talc and invasive and borderline cancers separately, and found that the risk was elevated for both tumour types but was significant only for invasive tumours. In addition, risk was similar across the major histological subtypes of ovarian cancer (serous, mucinous, endometrioid) (see Table 2.4). [Limitations of this study included the lack of information on use of talc.]

Cook *et al.* (1997) evaluated the association between use of genital powders or deodorants and the risk for ovarian cancer in a case–control study conducted in three counties of western Washington State, USA. Cases were aged 20–79 years at diagnosis, were diagnosed with borderline or invasive epithelial ovarian cancer between 1986 and 1988 and were identified using the population-based Cancer Surveillance System of western Washington. Controls were identified using random-digit dialling, were residents of the three counties of interest and were similar in age to the cases. Among 512 eligible cases identified, 329 were interviewed (64.3%) and 313 were included in the analysis [61.1%]. A total of 183 eligible cases were not interviewed due to death (104), physician or patient refusal (73) or loss to follow-up (six). An additional 16 cases who were interviewed were excluded from the analysis because of non-white race (seven) and unknown genital use of powder (nine). Among 721 women identified as potential controls, 521 were interviewed (72.3%) and 422 were included in the analysis [58.5%]. Reasons for excluding interviewed controls from the analysis included: non-white race (28), age greater than 79 years (five), history of bilateral oophorectomy (58), unknown oophorectomy status (four) and unknown genital use of powder (four). Information on powder use, including the type, method, frequency and duration of use, and the covariates of interest was collected during in-person interviews. Covariates considered to be potential confounders in multivariable analyses included age, education, income, marital status, body mass index, oral contraceptive use and parity. A history of 'any' lifetime genital powder use (perineal dusting, diaphragm storage, use on sanitary napkins or use of deodorant spray) was reported by 50.8% of cases and 39.3% of controls to yield an odds ratio of 1.5 (95% CI, 1.1–2.0) after adjustment for age. Among the individual methods of genital use of powder, risk was significantly elevated only for exclusive perineal dusting (odds ratio, 1.8; 95% CI, 1.2–2.9) after adjustment for age. In analyses adjusted for age and other types of genital use of powder, both perineal dusting (odds ratio, 1.6; 95% CI, 1.1–2.3) and genital deodorant spray (odds ratio, 1.9; 95% CI, 1.1–3.1) were associated with risk for ovarian cancer, while use of powder on a diaphragm or on sanitary napkins was not associated with an increased risk. There was no evidence of an increasing trend in risk with greater duration of perineal dusting, but a significant positive trend was noted for both duration (odds ratio, 2.7; 95% CI, 1.1–6.6 for > 12 cumulative lifetime months; *p* for

trend < 0.05) and number of lifetime applications (odds ratio, 2.6; 95% CI, 0.9–7.6 for > 500 lifetime applications; *p* for trend < 0.05) of genital deodorant spray. The effect estimates did not change materially when perineal use of dusting powder after the date of tubal ligation or hysterectomy was excluded. Risk was significantly elevated among women with any history of perineal dusting before 1976 (odds ratio, 1.8; 95% CI, 1.1–2.9), but the authors were unable to evaluate risk for use exclusively after 1976 due to the small number of women (four cases and 10 controls) who had had this exposure. Among the individual types of powder evaluated (cornstarch, talcum powder, baby powder, deodorant powder, scented body/bath powder), risk for ovarian cancer was non-significantly elevated for 'any' use of talcum powder (odds ratio, 1.6; 95% CI, 0.9–2.8) and bath/body powder use (odds ratio, 1.5; 95% CI, 0.9–2.4) after adjustment for age and other types of powder use (yes/no). The authors also evaluated the association between any genital use of powder and the risk for the major histological subtypes of ovarian cancer (see Table 2.4). Risk was significantly elevated for serous tumours (odds ratio, 1.7; 95% CI, 1.1–2.5) and all other tumour types (odds ratio, 1.8; 95% CI, 1.1–2.8) but not for mucinous or endometrioid tumours. [Limitations of this study included the relatively low participation rates among the cases and controls.]

Eltabbakh *et al.* (1998) compared risk factors among 50 cases of primary extra-ovarian peritoneal carcinoma (the 'study' group) and 503 cases of primary epithelial ovarian cancer (the 'control' group) treated at Roswell Park Cancer Institute in Buffalo, NY (USA), between October 1982 and October 1996. No healthy controls were enrolled in this study. Diagnoses were reviewed by staff in the Division of Pathology (study and control groups) and were confirmed by a single pathologist as part of another study (study group only). Information on reproductive history, menstrual history, use of hormones and contraceptives and personal hygiene was collected through a self-administered, 44-item questionnaire which all patients were asked to complete during the hospital admission process. All women who returned a questionnaire were eligible to be included in the study. Among these patients, the overall questionnaire response rate was 60%. Response was inversely correlated with severity of disease and response rates were similar for the two diagnoses included in this study. Because data on perineal talc use was missing for 37 patients in the 'control' group, only 466 ovarian cancer patients were included in the analysis. Women who had primary ovarian cancer were significantly more likely to report a history of perineal use of talc compared with women who had primary peritoneal cancer (48.1% versus 26.0%; [crude odds ratio = 2.6] $P = 0.003$). Among the other characteristics examined, only age and age at menarche differed significantly in the two groups. [Limitations of this study included the minimal information on talc use, the low questionnaire response rate among study participants, particularly among the patients with more advanced disease, the use of a self-administered questionnaire completed during the admissions process, which may have limited the quality of the responses, and the lack of a 'healthy' comparison group.]

Godard *et al.* (1998) evaluated risk factors for familial and sporadic ovarian cancer in a population of French Canadian women in Montréal, Quebec (Canada). Of 231 cases

who were identified between 1995 and 1996 at two gynaecological oncology clinics in Montréal, 183 (79.2%) were interviewed and 170 (73.6%) were included in the analysis. Reasons for non-inclusion were death ($n = 21$), refusal/unavailability to participate ($n = 12$), loss to follow-up ($n = 15$) and tumours were non-epithelial in origin ($n = 13$). All cases were between the ages of 20 and 84 years at diagnosis, with a mean age at diagnosis of 53.7 years and a mean age at interview of 55.9 years. Controls were identified using a modified random-digit dialling method and were frequency-matched to cases by age (within 1 year) and French Canadian ethnicity. The mean age at interview for the controls was 56.7 years. Among 750 households contacted regarding participation in the study, 66.7% ($n = 500$) either did not have an eligible female resident or did not reply to the researchers' inquiries and 10.7% refused to participate. A total of 170 women were interviewed and included in the analysis as controls. A standardized 57-item questionnaire was used to obtain information on the family, medical and reproductive history of each participant. Cases were interviewed either by telephone (30%) or in the study clinics (70%). No information was given on the methods of interview for control subjects. Information on family history of cancer was collected to determine whether risk factors differed for the sporadic and familial cases of ovarian cancer. Familial cases were those patients who had one or more family members (first, second or third degree relatives) with breast cancer diagnosed before 55 years of age or ovarian cancer diagnosed at any age. Sporadic cases were those patients who had no family members with breast cancer diagnosed before 55 years of age or with ovarian cancer diagnosed at any age. Perineal exposure to talc was assessed qualitatively (ever/never, with 'never' as the baseline). Covariates that were considered to be potential confounding variables were age at menarche, age at menopause, parity, age at first and last childbirth, duration of oral contraceptive use, age at last oral contraceptive use, tubal ligation, alcohol use and previous breast or abdominal surgery. Talc exposure was more common in cases than controls, with 10.6% of the cases and 4.7% of the controls reported perineal use of talc ($P = 0.06$). No difference between perineal use of talc was reported in the familial and sporadic cases ($P = 0.79$). Multivariate analyses were performed comparing all cases, (all, sporadic, familial) with controls. In these analyses, perineal use of talc was associated with a non-significant increase in the total risk for ovarian cancer (odds ratio, 2.5; 95% CI, 0.9–6.6; $P = 0.07$). Risk was similarly non-significantly elevated for sporadic (odds ratio, 2.5; 95% CI, 0.9–7.1) and familial cases (odds ratio, 3.3; 95% CI, 0.9–12.4) compared with the controls. [Limitations of this study included its small size and the lack of any detailed information on perineal use of talc. The control participation rates may have been low (although this is not clear) and it is not certain how representative the controls were.]

Cramer *et al.* (1999) analysed the association between genital exposure to talc and the risk for primary epithelial ovarian cancer among 563 cases and 523 controls residing in eastern Massachusetts and New Hampshire, USA. Cases were identified between May 1992 and March 1997 through hospital tumour boards or statewide cancer registries. Among 1080 cases diagnosed in this period (including borderline tumours), 203 (18.8%)

were excluded due to death, change of address, inability to speak English, no telephone in residence or a non-ovarian primary cancer. Of the 877 eligible cases remaining after these exclusions, 563 (64%) were included in the analysis. The remaining 314 cases were excluded because of physician refusal ($n = 126$) and patient refusal ($n = 136$). Pathology reports were reviewed to confirm the diagnoses for all cases, and slides were requested and reviewed in the case of discrepancies between the reported histology and the histology assigned based on the pathology report review. Controls were identified by random-digit dialling and town resident books (to identify additional women over the age of 60 years who lived in Massachusetts) and were frequency-matched to cases by age (within 4 years) and location of residence. Of the potentially eligible controls, 72% of those identified by random-digit dialling and 49% of those identified through town books agreed to participate. All study participants were interviewed in-person using a standardized questionnaire to obtain information on their medical and reproductive histories, family history and personal habits. The questionnaire also asked multiple questions on powder use, including route of exposure (application to non-genital areas, application to perineum, sanitary napkins or underwear, husband's use of powders in his genital area), brand of powder used (talc, cornstarch), age at first use, duration and frequency of use (< 30, 30–39, > 40 uses per month). Participants were asked about exposures that occurred at least 1 year before the date of diagnosis (cases) or the date of interview (controls). The results were adjusted for the following potential confounding variables: age, state of residence, body mass index, parity, oral contraceptive use, family history of breast or ovarian cancer and history of tubal ligation. The prevalence of talc use was higher among cases than controls; 44.6% of cases and 36.1% of controls reported 'any' use of talc (included use in both genital and non-genital areas) and 27.0% of cases and 18.2% of controls reported 'genital' use of talc (included dusting of perineum/sanitary napkins/underwear, either exclusively or in combination). Talc use in non-genital areas was not associated with risk when compared with women who did not use personal powder (odds ratio, 1.1; 95% CI, 0.8–1.5). However, genital use of talc was associated with a significant 60% increase in risk (odds ratio, 1.6; 95% CI, 1.2–2.2). Women who reported more than one method of talc use in the genital area had an even greater risk for ovarian cancer (odds ratio, 2.2; 95% CI, 1.3–3.6). No association was observed between genital use of talc and risk for ovarian cancer among women who had undergone tubal ligation after adjustment for age (odds ratio, 1.0; 95% CI, 0.5–2.1). Because of the low prevalence of use ($< 1\%$ of the study population) of cornstarch, evaluation of this product was uninformative. When women who had been exposed to powder only in non-genital areas were excluded from the analysis, no linear trend was observed between risk for ovarian cancer and age at first genital use of talc, duration of use, frequency of use or total number of lifetime applications. However, when non-genitally exposed women were included in the analysis, a significant linear trend was observed with increasing number of lifetime applications, after talc applications that occurred during non-ovulatory years or after tubal ligation or hysterectomy were excluded ($P = 0.02$). Additional findings of interest included: a non-significant increase in risk among married women with no

personal talc use whose husbands had used talc for genital hygiene (odds ratio, 1.5; 95% CI, 0.9–2.5); and a stronger association between genital use of talc and risk for ovarian cancer among women who had used talc before their first live birth (odds ratio, 1.6; 95% CI, 1.1–2.3) than for women who had used it exclusively after their first live birth (odds ratio, 1.0; 95% CI, 0.4–2.5). The association with genital use of talc was strongest for serous invasive tumours (odds ratio, 1.7; 95% CI, 1.2–2.4). No association was observed for endometrioid/clear-cell (odds ratio, 1.0; 95% CI, 0.7–1.6) or mucinous tumours (odds ratio, 0.79; 95% CI, 0.4–1.4) (see Table 2.4).

Wong *et al.* (1999) reported the results of a case–control study conducted at Roswell Park Cancer Institute, Buffalo, NY (USA) of 499 cases treated between October 1982 and October 1992 (largely those reported by Eltabbakh *et al.*, 1998) and 755 hospital-based controls. The controls were randomly selected from a registry of patients who were being treated for non-gynaecological malignancies and were frequency-matched to cases by age at diagnosis (within 5 years). The most common diagnoses among controls were colorectal (43.3%) and skin cancers (34.5%) and leukaemia (17.7%). All participants completed the self-administered, 44-item questionnaire that all patients were asked to complete during the hospital admission process. All analyses were adjusted for age at diagnosis, parity, oral contraceptive use, tobacco smoking, family history of ovarian cancer, age at menarche, menopausal status, income, education, geographical location and history of tubal ligation or hysterectomy. The analysis was restricted to 462 cases and 693 controls with information on perineal use of talc. 'Ever' use of talc (genital or non-genital) was reported by 47.8% of the cases and 44.9% of the controls, while use of talc in the genital or thigh area was reported by 34.0% of the cases and 32.2% of the controls. There was no association between any method of talc use and the risk for ovarian cancer after adjusting for several potentially confounding variables. The adjusted odds ratio for talc use in the genital or thigh area was 1.0 (95% CI, 0.8–1.3). Duration of talc use was similar in the cases and controls, and no association between talc use and the risk for ovarian cancer was found for any duration category. No significant association was observed between talc use and any of the major histological subtypes of ovarian cancer (see Table 2.4); the odds ratio for serous cystadenocarcinoma was 1.2 (95% CI, 0.7–2.1). No evidence was found of effect modification by history of tubal ligation or hysterectomy. Among women who had not undergone tubal ligation or hysterectomy, the odds ratio for the association between talc use and risk for ovarian cancer was 1.2 (95% CI, 0.8–1.6) while among women who had undergone tubal ligation or hysterectomy, the odds ratio was 0.8 (95% CI, 0.5–1.2). [Limitations of the study included the sparse information on talc use. In addition, the use of hospital controls with non-gynaecological malignancies may have caused selection bias. As noted in the earlier report by Eltabbakh *et al.* (1998), the response rate to the questionnaire was low in this study population, particularly among the patients with more advanced disease.]

Ness *et al.* (2000) examined whether factors related to an inflammatory response of the ovarian epithelium (such as exposure to talc, endometriosis, cysts and hyperthyroidism) played a role in the risk for ovarian cancer. The study was conducted

among 767 recently diagnosed cases of epithelial ovarian cancer and 1367 population-based controls. Cases were aged 20–69 years and were identified between 1994 and 1998 at 39 hospitals in the Delaware Valley region (USA). Of 1253 potentially eligible cases, 61.2% were interviewed and included in the analysis. Reasons for excluding women from the study included: diagnosis more than 6 months before the interview ($n = 296$), severe illness or death ($n = 69$), unavailability of contact information ($n = 15$), physician refusal ($n = 14$) or patient refusal ($n = 92$). Controls were identified through random-digit dialling (for controls ≤ 65 years of age) and Health Care Financing Administration lists (for controls 65–69 years of age) and were frequency-matched to cases by age and location of residence. Overall, 72% of the eligible potential controls agreed to participate in the study. A pathological review was conducted for a subset of the cases ($n = 120$). When compared with the original diagnosis, the central review was 95% concordant for invasiveness and 82% concordant for cell type. The original pathological diagnosis was used in the analysis for all cases. A standardized, 1.5-hour interview was conducted in the homes of the participants to collect information on menstrual and reproductive history, sexual activity, use of contraceptives, history and duration of talc use (genital and non-genital applications and exposure via male sexual partners). Talc use was categorized according to the method of application (never, feet, genital/rectal, sanitary napkins, underwear, diaphragm or cervical cap, or male partner) and duration of exposure (< 1 year, 1–4 years, 5–9 years, > 10 years). Unconditional logistic regression adjusted for age, parity, race, family history of ovarian cancer, oral contraceptive use, tubal ligation, hysterectomy and lactation was used in all analyses. A history of talc use in the genital/rectal area was reported by 161 cases [21.0%] and 219 controls [16.0%] to yield an adjusted odds ratio of 1.5 (95% CI, 1.1–2.0). Significant associations were also observed for the use of talc on sanitary napkins (odds ratio, 1.6; 95% CI, 1.1–2.3) and on underwear (odds ratio, 1.7; 95% CI, 1.2–2.4). The use of talc on the feet, arms or breasts was associated with a significant 40% increase in risk; however, women may also have used talc on more than one area of the body, including the genital and/or rectal area. Use of talc on diaphragms or cervical caps and use by a male sexual partner were not associated with the risk for ovarian cancer. There was no clear trend between risk for ovarian cancer and increasing duration of use of talc on the genital and/or rectal area or feet. Adjusted odds ratios of 2.0 (95% CI, 1.0–4.0), 1.6 (95% CI, 1.1–2.3), 1.2 (95% CI, 0.8–1.9) and 1.2 (95% CI, 1.0–1.5) were observed for < 1 year, 1–4 years, 5–9 years and ≥ 10 years of use, respectively. [Limitations of this analysis included the sparse information on talc use. In analyses of duration, the use of talc on the feet was also included as an exposure. The relatively low participation rates among cases was also a limitation of the study.]

Langseth and Kjaerheim (2004) (described in detail in Section 2.1.2*(b)*) evaluated the association between employment in the pulp and paper industry in Norway and the risk for ovarian cancer. In addition to the assessment of occupational exposure, information was collected on hygienic use of talc and potential confounders for a subset of the cases and controls during a personal interview conducted at the mills or by telephone. Exposure to hygienic talc products was categorized as ever/never for personal use on diapers,

sanitary napkins, underwear or husband's use in the genital area. Thirty-five cases and 102 of the eligible controls or their next of kin agreed to an interview and an additional 19 women who were not cases were interviewed and included in secondary analyses as supplementary controls. A family member completed the interview (due to the death of the case or control) for 25 of the cases and 31 of the controls. Use of talc on the genital area was reported by 12 cases and 53 controls to yield an odds ratio of 1.2 (95% CI, 0.4–3.2). [The primary limitations of this analysis were the small number of cases, the small percentage of cases and controls who were interviewed to obtain information on the covariates of interest and use of surrogate respondents to obtain information on covariates for the deceased cases and controls. The Working Group noted that hygienic exposure to talc was assessed retrospectively in the nested case–control study.]

Mills *et al.* (2004) evaluated the association between perineal exposure to talc and the risk for ovarian cancer in an ethnically diverse population from 22 counties of central California, USA. The study included 256 incident cases diagnosed between 1 January 2000 and 31 December 2001 and identified through two regional cancer registries using rapid case ascertainment procedures and 1122 controls identified by random-digit dialling. Controls were frequency-matched to the cases by age and ethnicity. Pathology reports were reviewed centrally for a subset of the cases to confirm the diagnosis, subtype and invasiveness of each cancer. Potential controls were ineligible for inclusion in the study if they were under 18 years of age, were not a resident of the counties of interest or if they had a history of epithelial ovarian cancer or bilateral oophorectomy. Among 652 cases identified during the study period, 263 (40.3%) were excluded due to: language or hearing difficulties ($n = 17$), death ($n = 76$), physician refusal ($n = 10$), severe illness ($n = 41$) or unavailability of current contact information ($n = 119$). Of the 389 eligible cases who were contacted regarding participation in the study, 256 (65.8%) agreed to participate and were interviewed. Of a total of 2327 potential controls, 740 (31.8%) were excluded from the study due to: age ($n = 80$), location of residence ($n = 21$), language difficulties ($n = 10$), previous bilateral oophorectomy ($n = 252$), severe illness ($n = 19$) or change of address or telephone number or inability to contact the woman after repeated attempts ($n = 358$). Of the 1587 potential controls who were contacted and found to be eligible, 1122 (70.7%) agreed to participate and were interviewed. All cases and controls were interviewed by telephone to obtain information on their medical history, covariates of interest and history of perineal exposure to talc, including the frequency, duration and calendar years of use. Information on talc use was unavailable for seven cases and 17 controls; thus, the final study population for this analysis included 249 cases and 1105 controls. For the final models, unconditional logistic regression adjusted for age, race/ethnicity, duration of oral contraceptive use and breastfeeding was used. Additional covariates considered to be potential confounders included family history of breast cancer or ovarian cancer, parity, history of pregnancy, body mass index, hysterectomy, tubal ligation and duration of postmenopausal use of hormones. A history of perineal talc use was reported by 42.6% of the cases and 37.1% of the controls to yield an adjusted odds ratio of 1.4 (95% CI, 1.0–1.9). A significant trend ($P = 0.015$) with increasing frequency

of talc use was observed. The greatest risk for ovarian cancer was observed among women with the highest frequency of use (odds ratio, 1.7 for use 4–7 times per week; 95% CI, 1.1–2.6). There was a borderline significant trend with increasing duration of use ($P = 0.045$). The highest risk was observed among women with 4–12 years of use (odds ratio, 1.9; 95% CI, 1.2–3.0) and elevated but non-significant risks were seen among women with longer durations of use with odds ratios of 1.5 (95% CI, 0.9–2.3) and 1.2 (95% CI, 0.7–2.1) for 13–30 and > 30 years of use, respectively. A borderline significant trend was noted for cumulative talc use (frequency times duration of use), although this was also not clear-cut ($P = 0.051$). The highest risks were observed in the second and third quartiles of cumulative talc use. When examined according to the time of use, the risk was higher among women who had first used talc after 1975 (odds ratio, 1.9; 95% CI, 1.3–2.9) than among those who had first used talc before or during 1975 (odds ratio, 1.2; 95% CI, 0.8–1.8). Risk was also higher among women who were aged 20 years or more at first talc use than among those who were under 20 years of age and among women who initiated talc use after their first birth than among those who had some use before their first birth. When time since last use was examined, women who had last used talc 1–2 years previously had the highest risk (odds ratio, 2.4; 95% CI, 1.4–4.1); women who had last used it 3–20 years previously had an elevated but non-significant risk for ovarian cancer (odds ratio, 1.6; 95% CI, 0.9–2.7). Modification of the association between perineal use of talc and risk for ovarian cancer by tubal ligation, hysterectomy, parity, oral contraceptive use, postmenopausal use of hormones and body mass index was also evaluated. Risk was higher among women who had not had tubal ligation (odds ratio, 1.5; 95% CI, 1.1–2.2) than among those who had (odds ratio, 0.9; 95% CI, 0.5–1.7), although the interaction was not statistically significant. Risk was also higher among women who had ever been pregnant (odds ratio, 1.4; 95% CI, 1.1–2.0) than among those who had never been pregnant (odds ratio, 0.9; 95% CI, 0.4–2.3) and among women who had no history of oral contraceptive use (odds ratio, 1.6; 95% CI, 1.0–2.6) than among those who had used oral contraceptives (odds ratio, 1.3; 95% CI, 0.9–1.8). No evidence was found of a modification of effect by hysterectomy status, body mass index or postmenopausal use of hormones. [Limitations of this study included the low participation rate and relatively small number of cases. In addition, pathology was not confirmed for all cases, which may have resulted in some misclassification of histological subtype.]

2.3 Use of talc in pleurodesis

The use of talc or iodized talc to produce pleurodesis began in the 1930s as a treatment for recurrent spontaneous pneumothorax or pleural effusions. The therapy involves the introduction of 0.5–10 g talc directly into the pleura using intrapleural injection. In recent decades, the therapy has most commonly been restricted to use for the treatment of malignant pleural effusions.

An individual case report described a lung adenocarcinoma that was diagnosed 2 years after pleurodesis with iodized talc (Jackson & Bennett, 1973).

A survey was reported (Research Committee of the British Thoracic Association and the Medical Research Council Pneumoconiosis Unit, 1979) of the long-term effects of pleurodesis with talc and kaolin among a series of British patients who were followed for 14–40 years. The one talc mentioned (BP Indian Finex) was reported not to contain fibrous amphiboles, but it was unclear if that was true of all the talcs used. Three lung cancers were observed (2.14 expected, $P > 0.3$) among 210 talc pleurodesis patients. Two of the lung cancer patients developed tumours on the opposite side from where treatment had occurred (18-month and 19-year intervals between treatment and death). The third patient had an oat cell carcinoma (site unknown) and died 32 years after treatment. No cases of mesothelioma were reported.

Viskum *et al.* (1989) reported on 99 Danish patients who had been treated in 1954–64 by pleurodesis with talc at doses that ranged from 0.5 to 4.9 g and who were followed for at least 20 years. Three deaths from lung cancer occurred [expected number of cases not provided], one on the side opposite from where treatment had occurred and two with no origin reported. No cases of mesothelioma were reported. [The Working Group noted that these reports are difficult to interpret because of the high prevalence of lung disease in the patient groups, which could be related to risk factors such as tobacco smoking. The type or source of talc used was not clear, although it was assumed to be pharmaceutical grade. No case of mesothelioma was observed but the number of expected cases would probably be very low.]

2.4 References

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3. Studies of Cancer in Experimental Animals

The Working Group identified an issue that relates to the interpretation of several of the inhalation and intratracheal instillation studies of talc. A lesion that is frequently seen in rats that have been exposed by inhalation to a range of poorly soluble particles such as talc has been described variously as 'proliferating squamous cyst', 'proliferative keratinizing cyst', 'proliferating squamous epithelioma', 'benign cystic keratinizing squamous-cell tumour' or 'cystic keratinizing squamous-cell tumour'. Various authors have included this lesion in tumour counts, but the neoplastic nature of this lesion has been debated (Kittel *et al.*, 1993; Carlton, 1994; Mauderly *et al.*, 1994; Boorman & Seely, 1995; Rittinghausen *et al.*, 1997; Rittinghausen & Kaspareit, 1998); its relationship to pulmonary neoplasia is uncertain.

The Working Group noted that, in many of the studies of 'talc' described below, no or limited characterization of the mineralogy of the sample employed was given, and, in particular, that there was a lack of information on fibre content or particle size.

3.1 Oral administration

Rat

Groups of 25 male and 25 female Wistar rats, 10 weeks of age, received about 50 mg/kg body weight (bw) per day of commercial talc [characteristics unspecified] in the diet (average survival, 649 days) or standard di*et al*one for life (average survival, 702 days). No significant difference in tumour incidence was found in the treated animals compared with control animals (Gibel *et al.*, 1976).

Groups of 16 male and 16 female Wistar-derived rats, 21–26 weeks of age, were fed 100 mg Italian talc (grade 00000; ready milled; mean particle size, 25 μm; containing 92% talc, 3% chlorite, 1% carbonate minerals and 0.5–1% quartz) per day per rat in the diet for 5 months (talc-containing diet was actually given for 101 days) and were then maintained on basal diet for life (average survival, 614 days). No differences in tumour incidence were noted between treated animals and eight male and eight female control animals fed basal diet throughout (average survival, 641 days) (Wagner *et al.*, 1977). [The Working Group noted the limited exposure period and the advanced age of the animals at the start of the study.]

3.2 Inhalation exposure

3.2.1 *Mouse*

Groups of 47–49 male and 48–50 female B6C3F$_1$ mice, 7 weeks of age, that were fed an NIH-07 diet, were exposed by inhalation to aerosols containing 0, 6 or 18 mg/m^3 MP 10–52 grade talc for 6 hours per day on 5 days per week for up to 104 weeks (dose equivalent, 0, 2 or 6 mg/kg bw per day for male mice and 0, 1.3 or 3.9 mg/kg bw per day for female mice). MP 10–52 grade is a high-purity microtalc (from a strip mine located in Missouri State, USA) that has a maximal particle size of 10 μm and is reported to contain no tremolite or any asbestiform minerals. After analysis, the talc was found to be free of asbestos and almost free of silica. The average mass mean aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) of the talc aerosols were calculated to be 3.3 ± 1.9 μm and 3.6 ± 2.0 μm for the 6- and 18-mg/m^3 chambers, respectively. At approximately week 70, difficulties were experienced in generating the talc aerosol, and the chamber concentrations were substantially lower than the target concentrations over a period of 12 weeks. Survival and final mean body weights of male and female mice exposed to talc were similar to those of the controls, and no clinical findings were attributed to exposure to talc. No significant increases in the incidence of neoplasms were observed. The incidence of pulmonary neoplasms (males: 27%, 11% and 23%; females: 11%, 12% and 6%) was similar between exposed and control groups of mice. [The Working Group noted that the incidence of alveolar/bronchiolar adenoma or carcinoma combined in historical control B6C3F$_1$ mice fed an NIH-07 diet in National Toxicology Program inhalation studies was 26.8% for males and 10.1% for females] (National Toxicology Program, 1993).

3.2.2 *Rat*

Two groups of 12 male and 12 female Wistar-derived rats, 6–8 weeks of age, were exposed by inhalation to a mean respirable dust concentration of 10.8 mg/m^3 Italian talc (grade 0000; ready milled; mean particle size, 25 μm in diameter; containing 92% talc, 3% chlorite, 1% carbonate minerals and 0.5–1% quartz) for 7.5 hours per day on 5 days a week for 6 or 12 months (cumulative exposures, 8200 and 16 400 mg/m^3 × h, respectively). Ten days after the end of each exposure period, six rats per group were killed; 12 rats per group died and two rats per group were unaccounted for; the remaining four rats per group were killed 1 year after the end of the exposure period. No differences were noted in the incidence of lung tumours compared with 24 male and 24 female untreated controls (Wagner *et al.*, 1977). [The Working Group noted the limited number of animals allowed to survive longer than 12 months after the end of each exposure period.]

Groups of 49 or 50 male and 50 female Fischer 344/N rats, 6–7 weeks of age, were exposed by inhalation to aerosols of 0, 6 or 18 mg/m^3 MP 10–52 grade talc (see Section 3.2.1) for 6 hours per day on 5 days per week until mortality in any exposure group

reached 80% (113 weeks for males and 122 weeks for females; dose equivalent, 0, 2.8 or 8.4 mg/kg bw per day for males GSD and 0, 3.2 or 9.6 mg/kg bw per day for females). The average MMAD and the GSD of the talc aerosols were calculated to be 2.7 ± 1.9 µm and 3.2 ± 1.9 µm for the 6- and 18-mg/m^3 chambers, respectively. At week 11, the chamber concentration for the 18-mg/m^3 group varied from approximately 30 to 40 mg/m^3 for a period of 7 weeks because of difficulties with the systems used to monitor aerosol concentration. In addition, at approximately week 70, difficulties were experienced in generating the talc aerosol for a period of 12 weeks during which the chamber concentrations were substantially lower than the target concentrations. The survival of treated male and female rats was similar to that of the controls. Mean body weights of rats exposed to 18 mg/m^3 were slightly lower than those of controls after week 65. Absolute and relative lung weights of male rats exposed to 18 mg/m^3 were significantly greater than those of controls at the 6-, 11- and 18-month interim evaluations and at the end of the lifetime study, while those of female rats exposed to 18 mg/m^3 were significantly greater at the 11-, 18- and 24-month interim evaluations and at the end of the lifetime study. Exposure to talc produced a spectrum of inflammatory, reparative and proliferative processes in the lungs. The principal toxic lesions observed included chronic granulomatous inflammation, alveolar epithelial hyperplasia, squamous metaplasia, squamous cysts and interstitial fibrosis of the lung. The authors considered that the squamous cysts represented a form of squamous metaplasia. The incidence of alveolar/bronchiolar adenoma and carcinoma (combined) in female rats was: control, 1/50 (carcinoma, 0/50); low-dose, 0/48; high-dose, 13/50 (carcinoma, 5/50) and was significantly greater ($P < 0.001$) in the high-dose group than in controls (carcinoma, $P = 0.028$). The incidence of pulmonary neoplasms in exposed male rats was similar to that in controls. Adrenal medulla pheochromocytomas (benign and malignant combined) occurred with a significantly positive trend in males (control, 26/49; low-dose, 32/48; high-dose, 37/47; $P = 0.007$) and females (control, 13/48; low-dose, 14/47; high-dose, 23/49; $P = 0.014$), and the incidence in the high-dose groups was significantly greater than that in controls ($P = 0.006$ for males, $P = 0.024$ for females). The incidence of malignant pheochromocytomas in females was: control, 0/48; low-dose, 1/47; high-dose, 10/49 ($P = 0.001$). Although adrenal medulla hyperplasia occurred with similar frequency among exposed and control females, the incidence of hyperplasia in exposed males was significantly lower than that in controls (National Toxicology Program, 1993). [The Working Group noted that some authors have indicated that stress and hypoxia may lead to a proliferation of chromaffin cells and eventually to pheochromocytomas. An increase in the incidence of these tumours was also observed in several other National Toxicology Program studies that used particulates and the same rat strain in which the background incidence of this type of tumour was quite high (Ozaki *et al.*, 2002; Melnick *et al.*, 2003). The Working Group also noted that this type of tumour was not reported in particle inhalation studies other than those of the National Toxicology Program, and hence felt that this increase may not be related to talc.]

3.2.3 *Hamster*

In a lifetime experiment, three groups of 50 male and 50 female Syrian golden hamsters, 4 weeks of age, were exposed by inhalation to an aerosol of talc baby powder that was prepared from Vermont talc by flotation (95% w/w platy talc with trace quantities of magnesite, dolomite, chlorite and rutile) for 3, 30 or 150 minute per day on 5 days a week for 30 days. The mean aerosol concentration was 37.1 mg/m^3, with a measurable respiratory fraction of 9.8 mg/m^3 and a MMAD of 4.9 μm. A sham-exposed group comprised 25 males and 25 females. Two further groups of hamsters, 7 weeks of age, were exposed to talc aerosol for 30 or 150 minute per day for 300 days. The mean aerosol concentration was 27.4 mg/m^3, with a measurable respiratory fraction of 8.1 mg/m^3 and a MMAD of 6.0 μm. Another sham-exposed group comprised 25 males and 25 females. The survivors of the last two talc-exposed groups were killed at the age of 20 months. At that time, 20% of the males were still alive and all females were dead. No primary tumours were observed in the lungs in any of the hamsters, although the incidence of alveolar-ccll hyperplasia in the groups given talc aerosol for 30 or 150 minutes per day for 300 days was 25% compared with 10% in the control group (Wehner *et al.*, 1977, 1979). [The Working Group noted the short daily exposure time and the high mortality rate.]

3.3 Intratracheal administration

Hamster

Four groups of 24 male and 24 female Syrian golden hamsters, 9 weeks of age, received 18 weekly intratracheal instillations of 3 mg talc (USP grade; silica oxide, 61–63%; magnesium oxide, 32–34%; other dusts, 0.85–1.06%; 93.3% <25 μm in diameter) in 0.2 mL saline with or without 3 mg benzo[*a*]pyrene, or 0.2 mL saline alone or were untreated. The animals were allowed to live out their lifespan (average 50% survival, 46–55 weeks). No respiratory tract tumours were observed in the talc-treated, saline-treated or untreated groups. Malignancies were observed in 33/45 animals treated with talc plus benzo[*a*]pyrene (Stenbäck & Rowlands, 1978). [The Working Group noted the short survival of the animals.]

3.4 Subcutaneous administration

Mouse

Fifty female R3 mice, 3–6 months of age, were given single subcutaneous injections of 0.2 mL of a mixture of 8 g talc [type unspecified] and 20 g peanut oil (delivered dose, about 80 mg) and were observed for life (average 50% survival, 596 days). No local tumour was observed (Neukomm & de Trey, 1961).

In a study reported in an abstract, female Marsh mice, 3 months of age, received single subcutaneous injections of 20 mg USP talc and were observed for 18–21 months. No tumour developed at the injection site in 26 treated animals or in 24 saline-injected controls (Bischoff & Bryson, 1976).

3.5 Intraperitoneal administration

3.5.1 *Mouse*

In a study that investigated the response to intraperitoneally injected asbestos, control groups of 12, four, five, six, five and 12 white male mice [age unspecified] were injected intraperitoneally with a 0.5-mL suspension (50%) of talc in saline and killed 26, 57, 112, 147, 170 and 343 days after injection, respectively. Talc was described as 6505–147–0000 Talc, USP V (no further analysis was made). Histopathological examination was performed, and no mesotheliomas or other neoplasms were reported (Jagatic *et al.*, 1967).

In a study reported as an abstract, female Marsh mice, 3 months of age, received a single intraperitoneal injection of 20 mg USP talc and were observed for 18–21 months. Intraperitoneal lymphoid tumours occurred in 5/22 treated animals and in 6/28 saline-treated controls (Bischoff & Bryson, 1976).

Fourty Swiss albino mice [sex unspecified], 6 weeks of age, received a single intraperitoneal injection of 20 mg ground commercial talc [type unspecified] in 1 mL saline. Within 6 months, 16 animals had died. In the 24 survivors allowed to live out their normal lifespan, three peritoneal mesotheliomas were observed, compared with 3/46 saline-treated controls (Özesmi *et al.*, 1985). [The Working Group noted the occurrence of mesotheliomas in saline-treated animals.]

3.5.2 *Rat*

A group of 40 female Wistar rats, 8–12 weeks of age, received four intraperitoneal injections of 25 mg granular talc [characteristics unspecified] in 2 mL saline at weekly intervals. A group of 80 female rats was injected with 2 mL saline alone and served as controls. The rats were observed until spontaneous death or when killed in moribund state. A mesothelioma was observed in 1/36 talc-exposed rats after 587 days compared with none in 72 controls (Pott *et al.*, 1974, 1976a,b).

In a study reported as an abstract, female Evans rats, 3 months of age, received a single intraperitoneal injection of 100 mg USP talc and were observed for 18–21 months. Of the treated rats, 3/27 developed tumours (one lymphosarcoma and one reticulum-cell sarcoma in the peritoneal cavity, one cystadenoma of the liver) compared with none of 26 saline-treated controls (Bischoff & Bryson, 1976).

3.6 Intrapleural and intrathoracic administration

3.6.1 *Mouse*

In a study reported as an abstract, male Marsh mice, 3 months of age, received a single intrathoracic injection of 10 mg USP talc. After 18–21 months, 5/47 treated mice had tumours (two adenocarcinomas and three lymphoid tumours of the lung) compared with none of 48 saline-injected controls (Bischoff & Bryson, 1976).

3.6.2 *Rat*

In a study reported as an abstract, female Evans rats, 3 months of age, received single intrathoracic injections of 50 mg USP talc. After 18–21 months, intrathoracic reticulum-cell sarcomas or lymphomas were observed in 7/30 talc-treated rats, 8/32 saline-treated rats and 7/28 untreated controls (Bischoff & Bryson, 1976).

In a lifetime study, a group of 24 male and 24 female Wistar-derived rats, 8–14 weeks of age, received a single intrapleural injections of 20 mg Italian talc (grade 00000; ready milled; mean particle size, 25 μm; containing 92% talc, 3% chlorite, 1% carbonate minerals and 0.5–1% quartz) in 0.4 mL saline. The mean survival time of the treated rats (655 days) was similar to that of 24 male and 24 female controls (691 days) that were injected with saline. No mesothelioma was detected in either group; one small pulmonary adenoma was found in one treated rat that died 25 months after injection (Wagner *et al.*, 1977).

Following thoracotomy, groups of 30–50 female Osborne-Mendel rats, 12–20 weeks of age, received intrapleural implantations of 40 mg of one of seven grades of refined commercial talc from separate sources in hardened gelatin. The rats were followed for 2 years, at which time survivors were killed. The incidence of pleural sarcomas was: talc 1, 1/26; talc 2, 1/30; talc 3, 1/29; talc 4, 1/29; talc 5, 0/30; talc 6, 0/30; talc 7, 0/29; untreated controls, 3/488 (0.6%); and controls that received implants of 'non-fibrous' materials described by the authors as 'non-carcinogenic', 17/598 (3%) (Stanton *et al.*, 1981).

3.7 Ovary implantation

Rat

In a study that investigated the effect of implanted talc on the rat ovary, a group of 10 female Sprague-Dawley rats, 10–15 weeks of age, received implants of 100 μL of a talc suspension in saline (100 mg/mL) onto the surface of the ovary by intrabursal injection. The talc was described as Italian 00000 (particle size, 0.3–14 μm) and contained no asbestos. Three sham-operated and three sham-treated control animals were included. Animals were killed after 12 months and histopathological examination of the ovaries was performed. Small focal areas of papillary change that were considered to be

preneoplastic changes were seen in the surface epithelium of 4/10 treated animals (0/6 controls). No neoplasms were reported (Hamilton *et al.*, 1984). [The Working Group noted that groups of animals implanted for 1, 3, 6 or 18 months were also included, but no results were reported for any of these groups.].

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4. Mechanistic and Other Relevant Data

The general principles of inhalation, deposition, clearance and retention of poorly soluble particles that have low toxicity are discusssed in the Monograph on carbon black in this volume.

4.1 Humans

4.1.1 *Deposition, retention and clearance*

Talc particles have been found at autopsy in the lungs of patients with 'talc pneumoconiosis' (Schepers & Durkan, 1955a; Seeler, 1959; Kleinfeld *et al.*, 1963; Abraham & Brambilla, 1980; Berner *et al.*, 1981; Vallyathan & Craighead, 1981). Talc, in the form of platy or elongated particles, has been found at autopsy in the lungs of urban residents, farmers and asbestos miners (Seeler, 1959; Langer *et al.*, 1971; Pooley, 1976; Gylseth *et al.*, 1984). Talc has been reported to be concentrated in lung scar tissue (Yao *et al.*, 1984). Clinically, intrapleural instillation of talc is used to induce pleural adhesions in cases of pleural effusion and pneumothorax (Rodriguez-Panadero & Antony, 1997).

Churg and Wiggs (1985) used transmission electron microscopy and energy dispersive X-ray spectroscopy to analyse the total fibrous and non-fibrous mineral content of the lungs of a group of 14 male smokers who had lung cancer but no history of occupational exposure to dust. A group of 14 control men were matched by age, smoking history and general occupational class. The average concentrations of mineral fibres and non-fibrous particles were nearly fourfold and approximately twofold higher, respectively, in the group with cancer than in the controls. Kaolinite, talc, mica, feldspars and crystalline silica comprised the majority of fibrous and non-fibrous particles in both groups.

In a subsequent study, Churg and Wiggs (1987) examined the distribution of mineral fibres in the lungs of 10 male smokers who did not have lung cancer or a history of occupational exposure to dust. The subjects were all over 50 years of age at death and had a smoking history that ranged from 15 to 100 pack–years (mean, 45±24 pack–years). The primary minerals identified were kaolinite, silica and mica and accounted for 64% of the fibres; feldspars and talc accounted for 9 and 7%, respectively. There was a significant correlation between smoking history and particle concentration (number of particles per gram of tissue) in the upper lobes. The diameters (mean±standard deviation [SD]) of talc particles in the upper and lower lobes were 1.2±0.9 μm and 0.9±1.0 μm, respectively.

Dumortier *et al.* (1989) used analytical electron microscopy to examine non-fibrous particle content in the bronchoalveolar lavage fluid of 51 occupationally

exposed subjects, six of whom were talc millers. In the latter group, two workers had almost exclusively talc in their lavage fluid, while the others had about 60% talc and 40% chlorite. In other workers, talc generally accounted for <3% of the particles in lavage fluid. It was noted that, although the exposure of one of the millers had ceased 21 years before the examination, talc particles were still present in his lavage fluid.

Talc particles have been found in stomach tumours from Japanese men (Henderson *et al.*, 1975), possibly due to ingestion of talc-treated rice (Merliss, 1971a,b). Talc particles, but apparently no other insoluble particles, were found in the subserosal stroma of hernia sacs, possibly due to ingestion of medications in which talc is present as a filler (Pratt *et al.*, 1985). Anani *et al.* (1987) reported the presence of talc fibres in the intestinal wall of a 46-year-old patient who had severe intestinal pain and was diagnosed with intestinal talcosis. A possible source of exposure was the talc contained in oral medications against tuberculosis, which the patient had taken nearly 20 years earlier over a period of 22 months (total intake of talc, 183 g).

Talc is often present as a filler in some materials used by drug addicts, which results in wide dissemination of talc particles to the lungs (Groth *et al.*, 1972; Lamb & Roberts, 1972; Farber *et al.*, 1981; Crouch & Churg, 1983), spleen, kidney, liver, brain, heart, adrenal and thyroid glands (Groth *et al.*, 1972) and even the retina (AtLee, 1972). In the lungs, most of the talc particles are found within the vessels of the alveolar walls, and are almost invariably associated with marked foreign-body granulomas (Crouch & Churg, 1983). The talc particles found in the lungs are larger after intravenous injection than after inhalation (Abraham & Brambilla, 1980) (see Section 4.1.2 for a discussion of the associated toxic effects).

In view of epidemiological evidence of a possible association between talc use for perineal hygiene and an increased risk for ovarian cancer (see Section 2), several studies have been conducted in women to determine potential retrograde movement of particles through the reproductive tract to the ovaries. These studies involved women who were about to undergo gynaecological surgery, mostly for diseases or complications of the reproductive tract and organs. Therefore, broad interpretations with regard to healthy women may be limited.

Egli and Newton (1961) found that inert carbon particles deposited in the vagina in two of three patients travelled to the fallopian tubes in about 30 minutes. De Boer (1972) concluded that Indian ink deposited below the level of the cervix is unlikely to travel quickly through the reproductive tract. In contrast, the findings of Venter and Iturralde (1979) and Mostafa *et al.* (1985) suggested that retrograde transport to the fallopian tubes is possible. Henderson *et al.* (1971) reported the actual presence of talc in histological specimens from 10 of 13 ovarian tumours, 12 of 21 cervical tumours and five of 12 normal ovarian tissues. Subsequently, Henderson *et al.* (1979) and Heller *et al.* (1996) provided further evidence of the presence of talc in the ovaries of women who had purportedly had perineal exposure to talc. However, in the latter study, no relation was found between talc-particle counts and reported perineal use of talc.

4.1.2 *Toxic effects*

The toxic effects of talc in humans are dependent on the route and dose of administration and the physicochemical properties of the talc. In addition, talc products commonly contain other potentially toxic minerals (see Section 1).

Talc pneumoconiosis is somewhat more prevalent and severe among people who are exposed to talc that contains asbestiform minerals than among those who are exposed to talc with no such impurities (Kleinfeld *et al.*, 1963). The form of this pneumoconiosis varies widely, from a simple asymptomatic type (Vallyathan & Craighead, 1981) to disabling conglomerate pneumoconiosis (Hunt, 1956; Graham & Gaensler, 1965; Miller *et al.*, 1971). Mixed-dust pneumoconiosis is frequently seen, including silicosis, asbestosis and occasionally other forms (Kleinfeld *et al.*, 1963; Mark *et al.*, 1979).

Several early reports described 'talcum powder granuloma' that arose from the use of talc on surgical gloves (reviewed in Eiseman *et al.*, 1947). Subsequent reports of cases have documented a variety of surgical complications, including adhesions, pseudotumours and sinus tracts that were attributable to exposure to talc (Lichtman *et al.*, 1946; Eiseman *et al.*, 1947; reviewed by Hollinger, 1990). Both skin granulomas and talc pneumoconiosis have been reported after liberal use of talc on the body (Tye *et al.*, 1966; Nam & Gracey, 1972; Wells *et al.*, 1979; Tukiainen *et al.*, 1984; Wehner, 1994).

Respiratory distress syndrome, which can be fatal, has been described in children following massive accidental inhalation of talcum powder (Cless & Anger, 1954; Molnar *et al.*, 1962; Lund & Feldt-Rasmussen, 1969; Gould & Barnardo, 1972) and in adult patients after talc pleurodesis (Rehse *et al.*, 1999).

A variety of pathological effects arise from the intravenous use by drug addicts of products that contain talc. These include micronuclear pulmonary opacities (Hopkins & Taylor, 1970; Arnett *et al.*, 1976; Waller *et al.*, 1980), angiothrombotic pulmonary hypertension (Wendt *et al.*, 1964; Paré *et al.*, 1979; Waller *et al.*, 1980) and conglomerate pulmonary lesions (Sieniewicz & Nidecker, 1980; Crouch & Churg, 1983). In addition, retinopathy, cerebral microembolization and granulomas of the liver, lymph nodes and kidneys have been reported (Min *et al.*, 1974; Paré *et al.*, 1979; Carman, 1985).

A series of cross-sectional studies reported from the New York State Department of Labour (Kleinfeld *et al.*, 1955, 1963, 1964, 1973) have documented talc pneumoconiosis in talc miners and millers, especially among tremolitic talc workers. The cases were associated with pleural plaques, restrictive or obstructive breathing disorders and decreased vital capacity of the lungs. The prevalence of disease was lower among those with lower cumulative exposure to dust and among those who processed granular rather than fibrous talc.

A series of cross-sectional studies that described talc pneumoconiosis in workers in talc mining, milling and manufacture in Italy (Rubino *et al.*, 1963; Tronzano *et al.*, 1965) found that the prevalence was related to extent and duration of exposure and that talcs contaminated with tremolite, serpentine and quartz were associated with significant pneumoconiosis.

One representative, well-controlled study among 80 workers exposed in the rubber industry to Vermont talc, which is reported to have a low content of silica and fibres, showed significantly increased respiratory symptoms, impaired ventilatory function and increased respiratory morbidity, but no radiographic abnormality (Fine *et al.*, 1976).

There has been some concern that talc may cause adult respiratory distress syndrome when instilled into the pleural space for pleurodesis (Rinaldo *et al.*, 1983; Bouchama *et al.*, 1984; Kennedy *et al.*, 1994; Rehse *et al.*, 1999; Light, 2000). Relatively recent cases were observed when talc was both insufflated and used as a slurry (Brant & Eaton, 2001; Scalzetti, 2001). However, other case series did not report the development of this disease (Weissberg & Ben-Zeev, 1993; Rodriguez-Panadero & Antony, 1997; Sahn, 2000; Ferrer *et al.*, 2001, 2002; Cardillo *et al.*, 2006). Many of the patients in the case reports had co-morbid conditions. [The Working Group noted that the talc used in these reports was not always characterized mineralogically and may have contained contaminants.]

The role of exposure to talc in the development of ovarian cancer has raised concerns (see Section 2). The normal ovarian epithelium is known to express several mucins that are protective against epithelial inflammation and injury (Lalani *et al.*, 1991; Gipson *et al.*, 1997; Ness & Cottreau, 1999; Taylor-Papadimitriou *et al.*, 1999; Ness *et al.*, 2000; La Vecchia, 2001). Several epithelial cancers, such as breast and ovarian cancer, express mucin (MUC-1) which is upregulated and aberrantly glycosylated in many carcinomas (Taylor-Papadimitriou *et al.*, 1999).

Cramer *et al.* (2005) examined the association between the characteristics of women with no previous diagnosis of ovarian cancer and levels of antibodies to MUC-1, a protein that is expressed by normal epithelial cells and overexpressed by ovarian cancer cells. The study participants were 705 controls from a case–control study of ovarian cancer conducted in Massachusetts and New Hampshire (USA) between 1998 and 2003. Plasma specimens collected from participants at enrolment into the study were analysed for anti-MUC-1 antibody levels using an enzyme-linked immunosorbent assay. Forty-eight cases of ovarian cancer with pre-operative blood specimens were also included in additional analyses; further 668 cases of ovarian cancer were included in the analyses to evaluate risk factors for ovarian cancer. Multivariable logistic regression, Spearman rank correlations and generalized linear models were used in the statistical analyses to determine which characteristics were associated with anti-MUC-1 antibody production and which were associated with the risk for ovarian cancer. Women who reported no previous genital use of talc were more likely to have antibodies to MUC-1 than women who had a history of regular genital exposure to talc (38.1% versus 28.6%; $P = 0.04$). In addition, there was a borderline significant trend between frequency of talc use and lower anti-MUC-1 antibody levels ($P = 0.11$), after adjustment for other characteristics that affect antibody levels. Several conditions associated with increased antibody production were associated with a decreased risk for ovarian cancer. The authors concluded that these findings suggest that the presence of anti-MUC1 antibodies is inversely correlated with risk for ovarian cancer. [Limitations of this study included the potential for bias in the participants' recollection of their genital use of talc, due to the case–control study design.

In addition, antibody levels in the cases and controls may not be comparable, since the presence of a cancer may affect anti-MUC-1 antibody levels.]

4.2 Experimental systems

4.2.1 *Deposition, retention and clearance*

The deposition, translocation and clearance of talc was investigated in 44 female golden Syrian hamsters (10 weeks of age) that were exposed by nose-only inhalation for 2 hours to 40–75 mg/m^3 neutron-activated talc (Johnsons's Baby Powder®, lot 228p; median aerodynamic diameter, 6.4–6.9 μm). The powder was high-grade cosmetic talc and consisted of 95% (w/w) platy talc mineral (Wehner *et al.*, 1977a). Alveolar deposition was approximately 20–80 μg, which represented 6–8% of the inhaled amount. The retention half-time of the talc deposited in the alveoli was 7–10 days, and alveolar clearance was reported to be essentially complete 4 months after exposure. No translocation of talc to liver, kidneys, ovaries or other parts of the body was found (Wehner *et al.*, 1977b). [The Working Group noted that the unusually short clearance time may be related to limitations in the sensitivity of the detection methods and the large size of the particles used.]

In rats exposed for 7.5 h per day on 5 days a week to aerosols of Italian talc (mean concentration of respirable dust [not further defined], 10.8 mg/m^3), the mean amounts of talc retained in the lung were 2.5, 4.7 and 12.2 mg per animal following exposures for 3, 6 and 12 months, respectively. These levels were approximately proportional to the cumulative exposures (Wagner *et al.*, 1977). In rats exposed for 6 hours per day on 5 days a week for 4 weeks to 2.3, 4.3 and 17 mg/m^3 respirable talc, the amounts retained in the lung at the end of exposure were 77, 187 and 806 μg talc/g lung, respectively (Hanson *et al.*, 1985).

Lung burdens of talc were determined in groups of 10 male and 10 female Fischer 344 rats and B6C3F$_1$ mice following exposure to asbestos-free talc for 6 hours per day on 5 days a week for 4 weeks. In rats exposed to 0, 2.3, 4.3 and 17 mg/m^3, average lung burdens were 0, 0.07, 0.17 and 0.72 mg talc/g lung, respectively. In mice exposed to 0, 2.2, 5.7 and 20.4 mg/m^3, average lung burdens of 0, 0.10, 0.29 and 1.0 mg talc/g lung, respectively, were observed. When normalized to the exposure concentration, the lung burden in mice was greater than that in rats and the normalized burden in rats increased with increasing exposure concentration (Pickrell *et al.*, 1989).

Conflicting data exist on systemic distribution following intrapleural instillation of talc (i.e. talc pleurodesis) in rats. Following administration of 10 or 20 mg talc [particle size unspecified] to rats (20 per group), talc was identified in the chest wall, lungs, heart, brain, spleen and kidneys. The authors concluded that talc is rapidly absorbed through the pleura and reaches the systemic circulation and organs 24 hours after administration (Werebe *et al.*, 1999). However, following instillation of 40 mg talc (median particle size, 31 μm) into 33 rats randomly assigned to autopsy 24 or 72 hours later, talc particles were

observed in only a few extrapulmonary organs, i.e. the brain, spleen and liver, but not the kidneys (Fraticelli *et al.*, 2002).

The systemic distribution of talc was investigated in rabbits following talc pleurodesis in two studies. In one study (Ferrer *et al.*, 2002), 10 rabbits received 200 mg/kg bw 8.4-μm asbestos-free talc particles and 10 received 200 mg/kg bw 12-μm talc particles. Five animals from each group were killed after 24 hours and five at 7 days after instillation. A tendency was seen for increased extrapulmonary distribution of the smaller particles, which were identified in the pericardium of 0/5 and 3/5 rabbits at 24 hours and 7 days, respectively. For the larger particles, one of five animals had talc in the pericardium at each time-point. Particles were identified in the liver of three of five animals exposed to the smaller particles 7 days after instillation; other groups had no particles in the liver. Small particles were found in the kidney of only 1/5 animals 24 hours after instillation. Both particle types were found in the spleen of 1/5 animals 24 hours after instillation. The results indicate that talc reached the lung parenchyma by breaking the mesothelial and elastic layer and that mobility was greater for the smaller particles.

In the other study, Montes *et al.* (2003) performed talc pleurodesis in rabbits (20 per group) at doses of 50 and 200 mg/kg bw of the small-particle talc used in the study by Ferrer *et al.* (2002). Doses were chosen to simulate treatment of a 60-kg patient with amounts of 3 and 12 g talc. The lung parenchyma of two and 14 rabbits of the low-dose and high-dose groups, respectively, contained talc. In the high-dose group, six of the animals had talc in the pericardium and five had talc in the liver; talc was not detected in these organs in the low-dose group. The results show that the systemic distribution of talc was dose-dependent.

In studies in rats, mice, guinea-pigs and hamsters that used radioactive tracer techniques, no intestinal absorption or translocation of ingested talc to the liver or kidneys was detected (Wehner *et al.*, 1977b; Phillips *et al.*, 1978). No translocation of talc into the ovaries was detected after single or multiple intravaginal applications of talc to rabbits (Phillips *et al.*, 1978) or monkeys (Wehner *et al.*, 1985, 1986).

4.2.2 *Toxic effects*

Reviews of the literature on the biological effects of talc in experimental animals are available (Lord, 1978; Wehner, 1994).

[The Working Group noted that in most of the studies of 'talc' described below, no or limited characterization of the mineralogy of the sample employed was given, and, in particular, information on fibre content or particle size was lacking.]

(a) Chronic toxicity

Mild to marked arterial endothelial cell proliferation with cellular encroachment into the lumen, the occurrence of occasional foreign-body giant cells within the endothelial masses and moderate thickening of the intra-alveolar septa of the lungs were observed

after intravenous injections of talc in rabbits and guinea-pigs (Puro *et al.*, 1966; Dogra *et al.*, 1977). No effect on the rat lung was observed after intravenous injection of talc (Schepers & Durkan, 1955b) but talc granulomas were seen in rats following intrasplenic injection of talc (Eger & Canaliss, 1964).

No chronic pathological effect was associated with oral administration of Italian talc (92% pure; 100 mg per day on 101 days over 5 months) to rats (Wagner *et al.*, 1977). Intratracheal injections of talc (total dose, 150 mg) into guinea-pigs induced perivascular and peribronchiolar focal accumulations of histiocytes, fibrocytes, plasma cells and eosinophils within 1 month. After 2 years, the dominant effects were bronchiolectasia, bronchiolitis and marked fibrosis (Schepers & Durkan 1955b).

Rats exposed to dust clouds of 30–383 mg/m^3 'industrial'- or 'pharmaceutical'-grade talc for 9 months developed chronic inflammatory changes including thickening of the walls of the pulmonary arteries and, eventually, emphysema (Bethge-Iwańska, 1971).

In rats exposed by inhalation to 10.8 mg/m^3 Italian talc (grade 00000; ready milled; mean particle size, 25 μm) for 3 months, minimal fibrosis was observed, the degree of which did not change during the observation period after exposure. Animals that were exposed for 1 year had minimal to slight fibrosis, the degree of which had increased to moderate within 1 year after cessation of exposure (Wagner *et al.,* 1977). In contrast, Syrian golden hamsters exposed to 8-mg/m^3 aerosols of cosmetic-grade talc for up to 150 minutes per day on 5 days a week for 30 days showed no histopathological change in the lungs, heart, liver, renal tissues, stomach or uterus (Wehner *et al.,* 1977c).

Two years after injection of 20 mg Italian talc (see above) into the right pleural cavity of rats, granulomas at the injection site were common, and one small pulmonary adenoma was observed, but no other relevant pathology was seen in the lungs (Wagner *et al.*, 1977).

Groups of male and female rats, 6–7 weeks old, were exposed to aerosols of 0, 6 or 18 mg/m^3 talc until mortality in any exposure group reached 80% (113 weeks for males and 122 weeks for females). These exposure concentrations provided a dose equivalent of 0, 2.8 or 8.4 mg/kg bw per day for male rats and 0, 3.2 or 9.6 mg/kg bw per day for female rats. The talc used for this study was MP 10–52 Grade (see Section 3.2.1) and was found to be free from asbestos by polarized light microscopy and transmission electron microscopy. Survival of male and female rats was similar to that of the controls. Mean body weights of rats exposed to 18 mg/m^3 were slightly lower than those of controls after week 65. No clinical findings were attributed to exposure to talc. Absolute and relative lung weights of male rats exposed to 18 mg/m^3 were significantly greater than those of controls at the 6-, 11- and 18-month interim evaluations and at the end of the lifetime study, while those of female rats exposed to 18 mg/m^3 were significantly greater at the 11-, 18- and 24-month interim evaluations and at the end of the study. Talc produced a spectrum of inflammatory, reparative and proliferative processes in the lungs. The principal toxic lesions observed included chronic granulomatous inflammation, alveolar epithelial hyperplasia, squamous metaplasia, squamous cysts and interstitial fibrosis of the lung. These lesions were accompanied by impaired pulmonary function characterized

primarily by reduced lung volumes, reduced dynamic and/or quasistatic lung compliance, reduced gas-exchange efficiency and non-uniform intrapulmonary gas distribution (National Toxicology Program, 1993).

Groups of male and female B6C3F$_1$ mice, 7 weeks of age, were exposed by inhalation to aerosols that contained 0, 6 or 18 mg/m^3 MP 10–52 grade talc (see Section 3.2.1) for up to 104 weeks (dose equivalents, 0, 2 or 6 mg/kg bw per day for male mice and 0, 1.3 or 3.9 mg/kg bw per day for female mice). Survival and final mean body weights of male and female mice exposed to talc were similar to those of the controls. No clinical findings were attributed to exposure to talc. Inhalation exposure to talc was associated with chronic inflammation and accumulation of macrophages in the lung. Accumulations of macrophages (histiocytes) containing talc particles were also observed in the bronchial lymph nodes (National Toxicology Program, 1993).

(b) In-vitro toxicity

A concentration >50 μg/mL Italian talc caused a 50% reduction in the colony-forming efficiency of cultured Chinese hamster V79-4 lung cells (Chamberlain & Brown, 1978).

The concentration of talc (99% pure) required to cause 50% haemolysis of red blood cells was 6.5 mg/mL, which is more than 50-fold that of chrysotile. A concentration of 0.1 mg/mL talc caused 35% release of ^{51}Cr from Syrian hamster tracheal epithelial cells labelled with radioactive sodium chromate; the concentration was twofold that required for chrysotile (Woodworth *et al.*, 1982).

Davies *et al.* (1983) examined the effect of different types of talc on mouse peritoneal macrophages *in vitro*. Macrophages were exposed to seven specimens of high-purity talcs and the release of lactate dehydrogenase and β-glucuronidase was measured. These enzymes are produced by macrophages after they digest materials that can induce fibrosis and chronic inflammation. Enzyme release after exposure of macrophages to quartz, a known fibrogenic dust, and magnetite, a non-fibrogenic dust, was also measured. Quartz caused the greatest cytotoxic reaction *in vitro*: the amount of enzyme released increased with the dose. Magnetite had no effect. All seven talc specimens were cytotoxic to the macrophages: the levels of enzymes released were dose-related but were lower than those observed after exposure to quartz. The results show that talc is cytotoxic to macrophages and may be able to induce fibrosis and chronic inflammation in animals. However, the macrophage response to talc appears to be weaker than that for other fibrogenic dusts such as quartz, and the response of macrophages to talc may be different *in vivo*.

Talc caused the release of several cytokines including C-X-C and C-C chemokines from normal human pleural mesothelial cells (Nasreen *et al.*, 1998). Pleural mesothelial cells exposed to talc did not undergo apoptosis, whereas malignant mesothelioma cell lines (ATTC CRL-2081, CRL-5820, CRL-5915) exposed to the same dose did (Nasreen *et al.*, 2000). Talc also caused the release of basic fibroblast growth factor in pleural mesothelial cells (Antony *et al.*, 2004).

In bone marrow-derived macrophages from mice, talc was found to stimulate DNA synthesis ([^{3}H]thymidine incorporation) (Hamilton *et al.*, 2001).

4.2.3 *Genetic and related effects*

Three samples of respirable talc failed to elicit significant unscheduled DNA synthesis (10, 20 and 50 µg/cm^2, 24 hours), sister chromatid exchange or aneuploidy (2, 5, 10 and 15 µg/cm^2, 48 hours) in rat pleural mesothelial cells, in contrast to various positive controls. The three samples, i.e Spanish talc (No. 5725), Italian talc (No. 5726) and French talc (No. 7841), contained 90–95% talc; the remaining contents were chlorite and dolomite. Electron microscopy analysis revealed that talc particles were taken up by the rat pleural mesothelial cells, but no aneuploidy was observed in metaphases (Endo-Capron *et al.*, 1993).

4.3 References

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5. Summary of Data Reported

5.1 Exposure data

The term 'talc' refers to both mineral talc and industrial mineral products that contain mineral talc in proportions that range from about 35% to almost 100% and are marketed under the name talc. Mineral talc occurs naturally in many regions of the world where metamorphosed mafic and ultramafic rocks or magnesium carbonates occur. Mineral talc is usually platy but may also occur as asbestiform fibres. (Asbestiform refers to a habit (pattern) of mineral growth and not to the presence of other minerals. Asbestiform talc must not be confused with talc that contains asbestos.) Together with platy talc, asbestiform talc is found in the Gouverneur District of New York State, USA, and occasionally elsewhere; it may be associated with other minerals as observed by transmission electron microscopy.

Talc products vary in their particle size, associated minerals and talc content depending on their source and application. Minerals commonly found in talc products include chlorite and carbonate. Less commonly, talc products contain tremolite, anthophyllite and serpentine.

Mineral talc is valued for its softness, platyness, inertness and ability to absorb organic matter. It is used in agricultural products, ceramics, paint and other coatings, paper, plastics, roofing, rubber, cosmetics and pharmaceuticals and for waste treatment. Cosmetic talc, which contains more than 90% mineral talc, is present in many cosmetic products and is used for many purposes, including baby powders and feminine hygiene products. The type of talc that is currently used for cosmetic purposes in the USA does not contain detectable levels of amphibole, including asbestos. It is not known whether this is true in other countries.

Workers are exposed to talc during its mining and milling. Reported geometric mean exposure levels to respirable dust are typically in the range of 1–5 mg/m^3. Workers may also be exposed in user industries, primarily in the rubber, pulp and paper and ceramics industries. Due to the presence of other particulates, exposure levels may be difficult to measure accurately. Consumer exposure by inhalation could occur during the use of loose powders that contain talc.

Accurate estimates of prevalence are not available. However, in some series of controls from epidemiological studies of ovarian cancer, the prevalence of use for feminine hygiene of body powders, baby powders, talcum powders and deodorizing powders, most of which contain cosmetic talc in varying amounts, has been reported to be as high as 50% in some countries. Perineal use for such purposes seems to have been a common practice in Australia, Canada, the United Kingdom, the USA and other countries, including Pakistan. Use of cosmetic talc in the USA has declined steadily since the late 1970s.

5.2 Human carcinogenicity data

The carcinogenic effect of exposure to talc not contaminated by asbestos fibres has been investigated in five independent but relatively small cohort studies of talc miners and millers in Austria, France, Italy, Norway and the USA. The miners and to a lesser extent the millers in these cohorts were also exposed to quartz. In a case–control study nested in the combined cohorts of talc workers from Austria and France, there was no tendency of higher risks for lung cancer by increasing cumulative exposure of workers to talc dust. In four of five studies, it was explicitly stated that no case of mesothelioma was observed. In the two studies from Italy and Norway, which included an estimate of cumulative exposure of the cohort to talc dust, the risk for lung cancer in the highest category was found to be close to or below unity. In the subgroup of miners in the study in the USA, an excess risk for lung cancer was found, which may be have been due to exposure in the workplace to radon daughters and quartz. In all the other groups of workers studied, there was no increased risk for lung cancer.

Female workers in the Norwegian pulp and paper industry had an increased risk for ovarian cancer, which, however, was attributed to exposure to asbestos. A community-based case–control study did not find an increased risk for ovarian cancer associated with occupational exposure to talc, but the prevalence of exposure was low.

Body powder containing talc has been used by women on the perineum (or genital area), on sanitary napkins and on diaphragms. In total, data from one prospective cohort study and 19 case–control studies were reviewed in the evaluation of the association of cosmetic talc use and the risk for ovarian cancer. The information collected on perineal talc use varied substantially by study (e.g. ever use versus regular use, and whether information on the mode of application, frequency or duration of use was available).

The cohort study was conducted among nurses in the USA and included 307 cases of ovarian cancer that occurred over 900 000 person–years of observation and a maximum of 14 years of follow-up. Information was collected on the frequency but not duration of regular use. Perineal use of talc was not associated with a risk for ovarian cancer.

The 20 case–control studies were conducted in Australia, Canada, China, Greece, Israel, Norway, the United Kingdom and the USA (nested case–control study), and included between 77 and 824 cases and 46 and 1367 controls. Five were hospital-based designs and the others were population-based studies. The Working Group designated a subset of these studies as being more informative based on the following characteristics: the study was population-based, was of a reasonable size, had acceptable participation rates and included information to allow control for potentially important confounders.

Eight population-based case–control studies from Australia, Canada (Ontario) and the USA (two non-overlapping studies in Boston, MA, and one each in California, Delaware Valley, eastern Massachusetts and New Hampshire and Washington State) were thereby identified as being more informative. The selected studies included at least 188 cases and had participation rates that generally ranged from 60 to 75%. Among these eight studies, the prevalence of use of body powder among controls ranged from 16 to 52%; however,

information on exposure was not collected in a comparable manner across studies. In addition, the frequency and duration of use or total lifetime applications were investigated in several studies as well as consideration of prior tubal ligation or simple hysterectomy. Only sparse data were available on whether women had used body powder before or after the mid-1970s.

The relative risks for ovarian cancer among users of body powder (versus non-users) were homogenous across this relatively diverse set of eight studies, each of which indicated a 30–60% increase in risk. Among the other 11 case–control studies, most also reported relative risks of this magnitude or higher. The subset of studies that assessed use of talc on a diaphragm were relatively uninformative due to their lack of precision.

Results on exposure–response relationships were presented in the cohort study and in seven of the more informative case–control studies. In the cohort study, no exposure–response trend was apparent. Positive exposure–response trends were apparent in the two Boston-based studies that presented the most comprehensive analysis. In the Canadian and Californian studies, a non-significant, weakly positive trend was observed for either duration or frequency of use, but not for both. In the other three case–control studies, no consistent trend was observed and the strongest associations tended to be seen among the shorter-term or less frequent talc users.

The cohort study and four of the eight more informative case–control studies presented results on histological type of ovarian cancer. When the analysis of the cohort study was restricted to the 160 serous invasive cases, a statistically significant increase in risk of about 40% was observed. The risk increased with increasing frequency of body powder use. Risks for serous ovarian cancer were somewhat greater than those for other histological types in two of the four case–control studies in which the contrast was reported. Results for other histological types were inconclusive.

The Working Group carefully weighed the various limitations and biases that could have influenced these findings. Non-differential misclassification of talc use, given the relatively crude definitions available, would have attenuated any true association. Although the available information on potential confounders varied by study, most investigators accounted for age, oral contraceptive use and parity. In most studies, only the adjusted relative risks were presented; however, in the three studies in which both age-adjusted and fully adjusted estimates were provided, relative risks did not differ materially, suggesting minimal residual confounding.

It is possible that confounding by unrecognized risk factors may have distorted the results. One or more such factors, if they are causes of ovarian cancer and also associated in the population with perineal use of talc, could induce the appearance of an association between the use of talc and ovarian cancer where there is none. In order for such an unrecognized risk factor to induce the consistent pattern of excess risks in all of the case–control studies, it would be necessary for the factor to be associated with perineal talc use across different countries and different decades. While the range of countries and decades covered by the more informative case–control studies is not very broad, it provides some

diversity of social and cultural context and thereby reduces the likelihood of a hidden confounder.

There was a distinct pattern of excess risk discernible in all of the case–control studies when users were compared with non-users; however, methodological factors needed to be considered. First, while chance cannot be ruled out as an explanation, it seemed very unlikely to be responsible for the consistent pattern of excess risks. A second possible explanation would be recall bias, to which case–control studies may be particularly susceptible. This may have been the case if there had been widespread publicity about the possible association between the use of body powder and cancer. In such circumstances, it is possible that women who had ovarian cancer could be more likely than women who did not to remember or over-report a habit, such as body powder use, if they thought that it may have played a role in their illness..There was a flurry of publicity in the USA in the mid-1970s concerning the possible risks for cancer posed by the use of talc-based body powders. Following an industry decision to market talc powders with no asbestos, it was the opinion of the Working Group that there had not been widespread public concern about this issue, at least until very recently. Therefore, the Working Group considered it unlikely that such a bias could explain the set of consistent findings that stretch over two decades. The Working Group believed that recall bias was a possibility inherent in the case–control studies and could not be ruled out. The Working Group also considered publication and selection biases and these were not judged to have substantially influenced the pattern of findings.

The Working Group searched for documentation on the presence of known hazardous minerals in talc-based body powders. There were strong indications that these products contained quartz in the mid-1970s and still do. There were also indications that occasional small concentrations of asbestos were present in these products before the mid-1970s, but the available information was sparse, sampling methods and detection limits were not described, and the range of locations where data were available was extremely limited. As a result, the Working Group found it difficult to identify a date before which talc-based body powders contained other hazardous minerals and after which they did not, or to have confidence that this would be applicable worldwide. In addition, the epidemiological studies generally do not provide information about the years during which the female subjects were exposed. Consequently, the Working Group could not identify studies in which an uncontaminated form of talc was the only one used by study subjects. Nevertheless, the Working Group noted that, even in the most recent studies in the USA, where exposure histories may have been much less affected by hazardous contaminants of talc, the risk estimates were not different from the early studies in which the possibility of such exposure was more likely.

To evaluate the evidence on whether perineal use of talc causes an increased risk for ovarian cancer, the Working Group noted the following:

- The eight more informative case–control studies, as well as most of the less informative ones, provided overall estimates of excess risk that were remarkably consistent; seven of these eight case–control studies examined exposure–response

relationships; two provided evidence supporting such a relationship, two provided mixed evidence and three did not support an association.

- The cohort study neither supports nor strongly refutes the evidence from the case–control studies.
- Case–control studies were susceptible to recall bias which could tend to inflate risk estimates but to an unknown degree.
- All of the studies were susceptible to other potential biases which could either increase or decrease the association.
- All of the studies involved some degree of non-differential misclassification of exposure that would tend to underestimate any true underlying association.

5.3 Animal carcinogenicity data

Talc of different grades was tested for carcinogenicity in mice by inhalation exposure, intrathoracic, intraperitoneal and subcutaneous injection, in rats by inhalation exposure, intrathoracic injection, intraperitoneal injection, oral administration and intrapleural and ovarian implantation, and in hamsters by inhalation exposure and intratracheal injection.

In male and female rats exposed by inhalation to a well-defined talc, the incidence of alveolar/bronchiolar carcinoma or adenoma and carcinoma (combined) was significantly increased in female rats. The incidence of adrenal medulla pheochromocytomas (benign, malignant or complex (combined)) showed a significant positive trend and the incidence in high-dose males and females was significantly greater than that in controls. The incidence of malignant pheochromocytomas was also increased in high-dose females. The Working Group did not consider it probable that the increased incidence of pheochromocytomas was causally related to talc but, based on the experimental data available, neither could talc-related effects be excluded.

Tumour incidence was not increased following the intrapleural or intrathoracic administration of a single dose of various talcs to rats. In two studies of intraperitoneal administration in rats, no increase in the incidence of mesotheliomas was observed. No increased incidence of tumours was produced in rats in two studies of talc administered in the diet or in another study of the implantation of talc on to the ovary.

Tumour incidence was not increased in mice following the inhalation of talc in one study, the intrathoracic administration of a single dose of various talcs in another study or the administration of talc by intraperitoneal injections in three studies. A single subcutaneous injection of talc into mice did not produce local tumours.

Tumour incidence was not increased following inhalation or intratracheal administration of talc to hamsters.

5.4 Mechanistic considerations and other relevant data

Different mechanisms are probably operative in the effects of talc on the lung and pleura, depending on the route of exposure.

In humans, deposition, retention and clearance of talc have been insufficiently studied, although talc particles have been found at autopsy in the lungs of talc workers.

In humans and experimental animals, the effects of talc are dependent on the route of exposure, and the dose and properties of the talc. Talc pneumoconiosis was somewhat more prevalent and severe among miners exposed to talc containing asbestiform minerals and/or asbestos than among those exposed to talc without such contaminants. However, the role of quartz and asbestos in the observed pneumoconiosis could not be ruled out. Among drug users, intravenous injection of talc present as a filler in the drugs resulted in microembolization in a variety of organs and alterations in pulmonary function.

In animal studies, talc has been shown to cause granulomas and mild inflammation when inhaled. Observations of the effects that occurred in the lungs of rats exposed by inhalation to talc suggested that the operative mechanisms may be similar to those identified for carbon black, and talc is known to cause the release of cytokines, chemokines and growth factors from pleural mesothelial cells.

In humans, intrapleural administration of talc as a therapeutic procedure results in pleural inflammation which leads to pleural fibrosis and symphysis. Pleural fibrosis is the intended effect of intrapleural administration of talc in patients with malignant pleural effusions or pneumothorax. Animal studies suggested that extrapulmonary transport of talc following pleurodesis increases with decreasing particle size and increasing administered dose. Talc has been shown to cause apoptosis of malignant cells *in vitro*.

Perineal exposure to cosmetic talc in women is of concern because of its possible association with ovarian cancer. Several studies have been conducted in women to assess potential retrograde movement of particles through the reproductive tract to the ovaries. These have been conducted in women who were about to undergo gynaecological surgery, most of whom had diseases or complications of the reproductive tract and organs that required surgery. The findings reported in these studies may be confounded by the various levels of dysfunction in clearance from the female reproductive tract due to underlying pathologies. In addition, most of the studies had little or no further information on the use of talc products for perineal hygiene or changes in habits that may have preceded surgery. On balance, the Working Group believed that the evidence for retrograde transport of talc to the ovaries in normal women is weak. In women with impaired clearance function, some evidence of retrograde transport was found. Studies in animals (rodents, langomorphs and non-human primates) showed no evidence of retrograde transport of talc to the ovaries.

In one study, predictors of the presence of antibodies to mucin protein were inversely related to the risk for ovarian cancer and exposure to powder containing talc.

No data were available on the genotoxic effects of exposure to talc in humans. The limited number of studies available on the genetic toxicology of talc *in vitro* gave negative results.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibres.

There is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder.

6.2 Cancer in experimental animals

There is *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibres.

6.3 Overall evaluation

Perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B)*.

Inhaled talc not containing asbestos or asbestiform fibres is *not classifiable as to its carcinogenicity (Group 3)*.

6.4 Rationale

In making this evaluation the Working Group considered the human and animal evidence as well as evidence regarding the potential mechanisms through which talc might cause cancer in humans.

The Working Group found little or inconsistent evidence of an increased risk for cancer in the studies of workers occupationally exposed to talc. The studies of talc miners and millers were considered to provide the best source of evidence, but no consistent pattern was seen. One study observed an excess risk for lung cancer among miners, but confounding from exposure to other carcinogens made it difficult to attribute this to talc and no excess risk was seen in millers. Other studies also found no increased cancer risk or no higher risk with increasing cumulative exposure. Overall, these results led the Working Group to conclude that there was *inadequate evidence* from epidemiological studies to assess whether inhaled talc not containing asbestos or asbestiform fibres causes cancer in humans.

For perineal use of talc-based body powder, many case–control studies of ovarian cancer found a modest, but unusually consistent, excess in risk, although the impact of bias and potential confounding could not be ruled out. In addition, the evidence regarding exposure–response was inconsistent and the one cohort study did not provide support for an association between talc use and ovarian cancer. Concern was also expressed that

exposure was defined in a variety of ways and that some substances called talc may have contained quartz and other potentially carcinogenic materials. A small number of Working Group members considered the evidence to be inadequate. Despite these reservations, the Working Group concluded that the epidemiological studies taken together provide *limited evidence* of an association between perineal use of talc-based body powder and an increased risk for ovarian cancer.

In one study of rats that inhaled talc, an excess incidence of malignant lung tumours was seen in females. The same study observed an excess incidence of pheochromocytomas in the adrenal medulla in both sexes, but the Working Group was divided as to whether these rare tumours could be attributed to exposure to talc. Other studies in rats and mice using different routes of administration did not find an excess of cancer, and two studies in rats were considered to be inadequate for evaluation. Based on the one positive study, the Working Group found that there was *limited evidence* of carcinogenicity of inhaled talc in experimental animals. There was no agreement within the Working Group as to whether the evidence on pheochromocytomas should be taken into account in the evaluation of animal data.